VOLUME 24 NUMBER 3

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STUDIES ON EPINEPHRIN. I

EFFECTS OF THE INJECTION OF EPINEPHRIN IN SOLDIERS WITH "IRRITABLE HEART" *

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AND

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LAKEWOOD, N. J.

With the mobilization of our troops, and especially the drafted troops, at the entrance of this country into the war, the problem of sorting the fit from the unfit was one of the first to come up. In attempting to solve this many other problems for the medical corps arose. Among these, one of the most interesting and at the same time one of the most baffling, was the problem of determining the etiologic factors of the symptom complex observed by DaCosta during the Civil war and described by him as the "irritable heart of soldiers." In the present war this condition has been termed by Lewis the "effort syndrome." As this problem has been studied more carefully, it has proved to be a many sided one, and it now seems quite certain that the symptom complex represents several clinical entities. Many opinions have been advanced as to the etiologic factors underlying this condition but few facts have been brought forward in their support. Thus hyperthyroidism has been held by some observers to be the chief factor, while many others regard it as at least a significant factor in the production of the symptom complex.

It was to determine the relation of the thyroid gland to this condition that a study of the basal metabolism in a number of these cases was begun at the U. S. Army General Hospital No. 9.[1] From this study it was concluded that hyperthyroidism did not play a significant rôle in the production of the symptom complex of "irritable heart of soldiers."

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* This investigation was suggested by and started under the direction of Major Francis W. Peabody, M. C., U. S. Army, and completed under the direction of Capt. Bertnard Smith, M. C., U. S. Army, at U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Peabody, Francis W., Wearn, Joseph T., and Tompkins, Edna H.: The Basal Metabolism in Cases of the "Irritable Heart of Soldiers," Med. Clin. North Am., September, 1918.

In order to make the investigation of the question of the rôle of the thyroid gland more comprehensive, it was decided to employ at the same time the epinephrin test. Goetsch has reported[2] that cases of hyperthyroidism give a very marked reaction to small doses of this drug. It was thought that the observations on the basal metabolism would form an interesting check on the value of the epinephrin test. It was soon observed that some of the cases with a normal basal metabolism and with histories not typical of hyperthyroidism showed a definite hypersensitiveness to epinephrin. This group of soldiers exhibited certain signs and symptoms which made them resemble superficially cases of the so-called "forme fruste" of exophthalmic goiter, and, indeed, many of them were sent to this hospital with a transfer diagnosis of hyperthyroidism. In addition to this group there were many other cases of so-called "irritable heart" which reacted abnormally to epinephrin but did not show any signs of hyperthyroidism. Inasmuch as this excessive reaction to epinephrin suggested a hypersensitiveness of the sympathetic autonomic nervous system, it was determined to make a more careful study of these patients.

LITERATURE

The literature concerning the action of epinephrin in man has been reviewed by Goetsch.[3] Frazier and Wilson,[4] working in England, made observations on ten cases of "irritable heart" and four normal men, following the injection of 0.01 gm. of epinephrin intravenously. They concluded that the sympathetic nervous system was more susceptible to the action of epinephrin in cases of "irritable heart" than in normal men.

PHYSIOLOGIC ACTION OF EPINEPHRIN

The physiologic action of epinephrin has been worked out experimentally in animals and to some extent by injection in man, but despite the large amount of work done there still remain many details of its actions which are not clear. It seems to be generally accepted, however, that epinephrin has a selective action on the sympathetic autonomic nerve terminals. It is on this fact that the interpretation of this work is based.

TECHNIC

The technic followed is the same as that used by Goetsch in studying the hypersensitiveness to epinephrin of patients with exophthalmic goiter. The patients remain at absolute rest in bed for a period of

2. Goetsch, E.: Newer Methods in the Diagnosis of Thyroid Disorders: Pathological and Clinical, New York State J. M. **18**:259 (July) 1918.

3. Loc. cit.

4. Frazier, Francis, and Wilson, R. M.: The Sympathetic Nervous System and the "Irritable Heart of Soldiers," Brit. M. J. **2**:27 (July 13) 1918.

one hour. If there is restlessness or apprehension they should be reassured, and every effort made to obtain mental as well as physical quiet. At the end of the rest period control readings of the blood pressure, pulse and respiratory rates are made at five minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation, or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium, or over the precordium, and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood pressure and heart rate are normal, or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia, or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venepuncture was done at the end of the rest period for blood sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed.

After satisfactory control readings have been made, 0.5 c.c. of a 1 : 1,000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding one $\frac{3}{200}$ grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1 : 1,000 solution.

After the injection four or five readings are made of the blood pressure, pulse and respiratory rates at two or three minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations, readings are continued at five minute intervals until one hour after the injection, when ten minute readings are made for a period of one-half hour, thus making the observation period one and one-half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time.

REACTION TO EPINEPHRIN

A typical positive reaction manifests itself on the average of about twelve minutes after the injection by a rise in systolic blood pressure, increased pulse rate and certain characteristic changes in the subjective and objective conditions of the patient. There may be restlessness, complaints of nervousness, precordial pain, palpitation, and frequently apprehension. Pallor or flushing may be present. A fine tremor is very characteristic, and while it usually only involves the hands it may become general and very marked, occasionally to the extent of shaking the bed. In a number of cases there was tremor of the eyelids. The hands usually become cold and often there is excessive sweating, especially in the palms. In some cases there was a definite dilatation of the pupils, while in others little change could be observed. Pulsation was frequently very marked in the neck and epigastrium and over the precordium. The patient often states that he experiences about the same symptoms that he had previously noted after exertion. The conditions just mentioned are very characteristic, and when they are present a hypersensitiveness to epinephrin is easily recognized without the aid of the blood pressure or pulse record.

The onset of the symptoms is usually simultaneous with the changes in blood pressure and pulse, and the symptoms vary in intensity with the changes in them. In a study of seventy-one charts of positive reactions in all types of "irritable heart" the average systolic blood pressure rise was found to be 24.5 mm. Twenty-five of these cases showed a rise of from 10 to 20 mm., twenty-six from 20 to 30 mm., sixteen from 30 to 40 mm., two from 40 to 50 mm., and in two cases the rise was over 50 mm., one being 52 mm. and the other 71 mm. The pulse pressure is increased in all of the positive cases, either the diastolic pressure remaining constant while the systolic pressure rises, or what is more characteristic, the diastolic pressure falling during the height of the reaction and returning to normal with the drop in systolic blood pressure.

In a study of the pulse curve in seventy-one positive cases the average increase in pulse rate was found to be 26 to the minute. Four cases showed an increase in pulse rate from 1 to 10, twenty-seven from 10 to 20, twenty-one from 20 to 30, thirteen from 30 to 40, six from 40 to 50, the greatest increase being 46. During the course of some of the positive reactions various pulse irregularities have been noticed. Among the conditions observed have been marked sinus arrhythmia, extrasystoles and dropped beats. These findings were confirmed by electrocardiograms. A careful electrocardiographic study has been made following the injection of epinephrin and will be reported in a separate paper by Lieut. Harry D. Clough.

Observation of the respiratory rate and depth of respirations has been of little value in interpreting the reaction. The rate may be increased or decreased. In a number of cases there was slowing with an increase in depth of respiration, while in a few cases there was an increase to the remarkable rate of forty or fifty with very shallow breathing. In a study of the gaseous metabolism following the administration of epinephrin, which is reported in a separate paper,[5] the minute volume of air breathed was found to be increased in each case. In these same patients pneumographic tracings showed either an increased respiratory rate or an increase in the depth of respiration.

The onset of the reaction occurs about twelve minutes after the injection; the height is reached on the average in thirty-two minutes and the reaction is finished in approximately one hour. The effect of the epinephrin is transitory and the symptoms experienced are rarely worse than those induced in the patient by exercise.

Usually the reaction is clean-cut and no difficulty is experienced in its classification as it is either clearly positive or negative. There is, however, a small group of cases in which the reaction is less definite and the correct interpretation can be made only after a careful study of the entire clinical picture. Finally, there remains a still smaller number of cases which it is impossible to classify as either negative or positive, and this type of reaction has necessarily been designated as doubtful. In such cases the test has usually been repeated, but the second test has always been a repetition of the first. As an aid to the interpretation of the reaction the observations made during the test may conveniently be divided into three parts as follows:

1. Symptoms (precordial pain, nervousness, palpitation, etc.), and certain objective conditions as throbbing, pallor, flushing, cold extremities, tremor and sweating.
2. Blood pressure.
3. Pulse rate.

In a large number of cases changes in all three were present and the reaction was easily determined. In a very few cases there were fairly marked changes in blood pressure and pulse rate without subjective symptoms. In each case with subjective changes of importance, however, there was a corresponding change in pulse and blood pressure.

In an endeavor to interpret correctly the more or less doubtful cases, a study of the positive and negative reactions was made, and the following rule formulated: A positive reaction is characterized by

5. Tompkins, Edna H.; Sturgis, Cyrus, C., and Wearn, Joseph T.: The Effects of Epinephrin Upon the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Men, Arch. Int Med., this issue, p. 269.

a rise in blood pressure of 10 mm. or more, associated with a rise in pulse rate of at least 10 to the minute, provided these are not isolated rises, and associated with the signs and symptoms such as tremor, pulsation, nervousness, precordial pain, dizziness or restlessness. It is impossible to make any statement that will definitely classify all cases, but the above, in our experience, has proved very satisfactory, except in those few cases with a fairly marked rise in blood pressure and pulse rate, without other changes. These have been regarded as positive reactions.

To meet the criticism that changes which might be interpreted as a positive reaction could result from the stimulus of an intramuscular injection in a nervous individual, several patients known to be sensitive to epinephrin were given the test according to the usual technic except that sterile water instead of epinephrin was given intramuscularly. There were no changes of importance in the hour and a half period following. At the end of this period, these patients were given the usual dose of 0.5 c.c. of a 1 : 1,000 solution of epinephrin, which produced a typical positive reaction with all of the classical signs. As further evidence that a painful stimulus will not produce changes indicating a positive reaction, it was noted that when venepuncture to secure blood for sugar determinations was done on ten epinephrin sensitive cases immediately before the epinephrin was injected it did not cause any change in the blood pressure, pulse or objective or subjective conditions of the patient. In a few cases a slight change has resulted in the blood pressure and pulse rate immediately following the epinephrin injection, but this was probably psychic. This change is easily distinguished from the effect of the epinephrin by its early occurrence, while the epinephrin effect usually appears about twelve minutes after the injection. Furthermore, the change is transitory, rarely persisting more than one observation while the true epinephrin effect is in the form of a curve.

OBSERVATIONS ON NORMAL SOLDIERS

In order to control the epinephrin test properly, it was necessary to determine the effect of 0.5 c.c. of a 1 : 1,000 solution of epinephrin in normal men. To do this, permission was obtained from the division surgeon and commanding officer of the 109th Sanitary Train, then stationed at Camp Dix, to try the test on twenty-six men of that organization who volunteered for that purpose. These men were not picked men, but all who offered themselves were accepted; they had, however, been through fourteen months of military training and were in excellent physical condition. In not a single case was there a positive reaction to epinephrin as judged by the rule formulated to deter-

mine a positive or negative case. The blood pressure and pulse curves showed slight, if any, change, and the characteristic subjective and objective conditions of the epinephrin sensitive group were lacking. In distinct contrast to the epinephrin sensitive patients with their marked restlessness and anxiety, the controls remained perfectly quiet, some of the men reading throughout the greater part of the test, while others actually slept.

In a detailed study of the records of the twenty-six men the following facts were determined:

1. *Systolic Blood Pressure.*—There was a rise in the systolic blood pressure in twenty-one of the twenty-six cases, the rise being small, usually between 6 and 12 mm. In five cases, the rise was over 12 mm., and in one case it reached 18 mm. The average rise for the twenty-six cases was 7 mm.

2. *Pulse Pressure.*—In fourteen of the twenty-six cases there was a measurable increase (over 5 mm.) in the pulse pressure. The increase was usually between 10 and 12 mm.; there were two cases with an increase over 12 mm., both being 18 mm.

3. *Pulse Rate.*—Of the twenty-six cases, sixteen showed an increase in pulse rate of over five beats to the minute. The average of the pulse rate increase was six for all of the cases.

4. *Respirations.*—Here it is difficult to draw conclusions, as twenty-one of the twenty-six cases showed an increase of from one to eight to the minute, but in nine cases there also was a drop. In two cases there was a drop and in two cases no change.

5. *Symptoms and Signs.*—There was slight pulsation in sixteen of the twenty-six cases, ten showed slight tremor of the hands, seven flushing, and three transitory pallor. In only two cases were there subjective symptoms, one man complaining of slight nervousness and the other of weakness. In all of the cases the pulsation, tremor, pallor and flushing were of a minor degree and of very short duration. Hence, it is seen that while the normal man may show slight changes following the injection of a small dose of epinephrin, all of the changes are of such a minor degree that they could not possibly be confused with an epinephrin positive reaction. They are never in the combination or of the intensity seen in epinephrin sensitive individuals.

CLINICAL STUDIES

A large proportion of the patients with "irritable heart" in General Hospital No. 9 were sent to the hospital from camps in the United States where they had developed symptoms of the "effort syndrome" early in their military career. As will be seen, the symptoms existed

TABLE 1.—Clinical Chart of—

No.	Name	Hospital Number	Age	Race	Military Service	Active Duty	Symptoms Causing Patient to Fall Out	Occupation	Character of	Time Lost From Work
1	M. C. H.	2677	30	U. S.	5½ months	1 day	Fainted	Clerk (bookkeeper)	Light	3 to 4 days a month in past year
2	B. S.	1103	20	U. S.	12 months	6 months	Palpitation, precordial pain	Dairy worker	Light	None
3	J. J. H.	766	23	U. S.	14 months	1 month	Dyspnea and precordial pain	Mechanical engineer	Light	None
4	A. M.	875	23	U. S.	3½ months	1 week	Fainted	Cook	Light	No work for 2½ years
5	W. C. S.	1149	25	U. S.	4 months	3 days	Precordial pain, dyspnea and dizziness	Railroad hostler	Light	About 1 month in 7
6	G. W. C.	1354	25	U. S.	10 months	1 week	Dizziness, dyspnea, palpitation	Student	Light	None
7	L. F. B.	2860	24	U. S.	5½ months	1 week	Dyspnea, palpitation, fainted	Barber	Ligth	2 days a week for past 2 years
8	E. M. H.	775	23	U. S.	19 months	12 months	Precordial pain dyspnea	Milkman	Light	None
9	S. H. G	1284	26	U. S.	7 months	2 days	Weakness, dizziness	Assistant cashier	Light	About 10 days a year
10	E. M.	2487	24	U. S.	6 months	3 weeks	Palpitation, dyspnea, weakness	Drug clerk	Light	About 1 month a year
11	O. R. S.	2569	19	U. S.	14 months	4 months	Precordial pain	Auto mechanics helper	Very light	About 3 weeks a year
12	A. M.	926	24	Russian Jew	5½ months	2 weeks	Precordial pain, dyspnea, weakness	Tailor	Light	Worked less than half time for past 3 years
13	G. S.	1110	23	U. S.	16 months	2 weeks	Dizzy, precordial pain, dyspnea, weakness	Shoecutter	Very light	3 or 4 days a month for past 5 years
14	F. K.	819	26	U. S.	10 months	6 months	Fainted	Printer	*	*
15	A. W.	1144	28	U. S.	3½ months	None	Pain in side	Hopper fitter	Light	1 week a month for past 4 years
16	R. D.	1185	23	U. S.	3½ months	3 weeks	Weakness, precordial pain	Printer	Light	1 day in 2 months
17	G. A.	729	24	U. S.	10 months	2 weeks	Pain in back and feet, dyspnea	Sailor	Light	Stopped at work frequently
18	J. F. F.	423	23	U. S.	12 months	2 months	Dyspnea	Freight checker	Light	1 day a week
19	C. R. B.	723	23	U. S.	12 months	6 months light duty	Precordial pain	Shoe worker	Light	2 to 3 days a month
20	J. C. F.	2587	26	U. S.	18 months	7 months	Dyspnea, precordial pain, dizziness	Manager retail grocery	Moderate	None
21	G. S.	929	29	Austria	6 months	None	Precordial pain	Weaver	Light	1 week in 3
22	D. R.	1109	22	U. S.	13 months	2 weeks	Dyspnea, pain in the legs	Waiter	Light	Frequently lost time
23	C. H.	405	28	U. S.	5 months	2 days	Precordial pain, dizziness	Drove garbage wagon	Light	About 3 days a week
24	G. H.	1227	31	U. S.	6 months	2 weeks	Dizziness and pain in stomach	Furniture repairer	Light	Lost much time
25	I. G. Z.	1230	23	U. S.	4 months	5 weeks	Dizzy spells and headache	Farmer	Very light	Occasionally
26	C. H. H.	949	24	U. S.	12 months	3 weeks	Dyspnea, weakness	Railroad clerk	Light	2 to 5 days a month
27	W. H. P.	2580	30	U. S.	18 months	9 months light duty	Precordial pain abdominal pain	Hat maker	Light	Several days a month
28	E. I. K.	1226	23	U. S.	4½ months	2 weeks	Weak spells "heart rapid"	None for 4 years	.....	.....
29	W. D. B.	1167	23	U. S.	4 months	12 days	Dizziness and nausea	Farmer	Light	Frequently lost time
30	D. C.	1148	26	Irish	3 months	2 weeks	Dyspnea and exhaustion	Chauffeur	Light	Worked 2 hours daily
31	J. K.	1177	31	U. S.	12 months	6 weeks	Precordial pain, nervousness	Shipping clerk	Light	2 to 3 days a month
32	H. R.	1251	24	U. S.	5 months	9 days	Palpitation, precordial pain	Machinist	Light	Lost weeks at a time

—Epinephrin Positive Patients

Exercise	Education	Special Points of History	Duration of Symptoms	Alleged Etiology	Weakness	Dizziness	Blurred Vision	Fainting	Excitability	Nervousness	Dyspnea	Precordial Pain	Special Symptoms	Remarks
None	3 years high school, bus. coll. 10 mo.	Always frail	5 years	"Worry"	+	+	0	+	+	+	+	+	Palpitation	Sick a great deal as child, never strong
Baseball but always short of wind	4th grade at 14 years	Good health strong	7 months	"Mumps"	0	+	+	0	+	+	+	+	Palpitation	
Always athletic	3 years high school	Good health	9 months	"Heavy cold"	+	+	+	0	+	+	+	+	Palpitation	
None as a rule	5th grade at 14 years	Left testicle removed 1916	3 years	None	+	+	+	+	+	+	0	+	Abd. and pain in back	
Baseball a little, none for 3 years	6th grade at 14 years	Never strong	11 years	"Injury to head"	+	+	+	0	+	+	+	+	.....	Healthy until 11 years ago
None	3 years law school	Always had to be careful	18 years	"Pneumonia at 7 years"	+	+	+	+	+	+	+	+	Palpitation	
None for 2 years	Finished high school at 18 years	Always frail	2½ years	"Heavy work"	0	+	+	+	+	+	+	+	Palpitation	Asthma since childhood
Always athletic	6th grade at 14 years	Always strong	7 months	"Worked too hard"	0	+	+	+	+	+	+	+		
Light exercise	Finished high school	Knew he was not equal to the work	8 months	"Overwork"	+	+	+	+	+	+	+	+	.....	Walked 21 miles in a day, 1 yr. ago
None	8th grade at 17 years	.....	4½ years	None	+	0	+	0	+	+	+	+	"Fast heart"	
None	8th grade at 16 years	Always sickly	16 years	"Sick when a baby"	+	+	+	+	+	+	+	+		
None	None	Never able to work hard	4 years	None	+	+	+	0	+	+	+	+	Palpitation	
Very light rarely	8th grade	Always weak and nervous	4 years	"Inside work"	+	+	+	0	+	+	+	+		
"	"	"	4 months	"	+	+	..	+	..	..	+	"	"	"
None	4th grade at 11 years	Always weak, doctored 7 years	All his life	"Working in hot room"	+	+	+	+	+	+	+	+	.....	Always weak
Breathing exercises	2 years high school	Always favored	Lifetime	None	+	+	+	+	+	+	+	+	.....	Weakness main symptom
None	2d grade at 16 years	.....	5 years	"Typhoid"	+	+	+	+	+	+	+	+	.....	Short of wind from feeling in throat
None	2 years high school	.....	Lifetime	"Born with it"	+	+	+	0	+	+	+	+	.....	Always weak and nervous
Very little	2 years high school	.....	6 years	None	+	+	+	+	+	+	+	+	.....	Pain left chest and shoulder
None	8th grade	Always healthy	1 year	None	+	+	+	+	0	0	+	+	Swelling of hands and feet	
None	9 years in Austria	"Coughed and spit blood"	4 years	"Cough and malaria"	+	+	+	+	+	+	+	+	Irritable	
None	5th grade at 14 years	.....	Lifetime	"Inherited"	+	+	+	+	+	+	+	+	Always nervous and weak	
None	3 or 4 years in school	.....	Lifetime	"Inherited"	+	+	+	+	+	+	+	+	Weak legs	
Walked 1 mile daily	2d grade	.....	Lifetime	None	+	+	+	0	+	+	+	+	.....	Flat feet
Walked 3 miles daily	Finished high school	.....	Lifetime	"Mother had TB when he was born"	+	+	+	0	+	+	+	+		
None	1 year college	.....	Since entering army	"Army work"	+	+	+	+	+	+	+	+	Swelling in the neck	
Could not stand it	8th grade	.....	Lifetime	None	+	+	+	0	+	+	+	+		
None	4th grade at 14 years	.....	7 years	"Nocturnal emissions"	+	+	+	0	+	+	+	+		
None	3d grade	Chorea in childhood	Lifetime	"Meningitis when baby"	+	+	+	+	+	+	+	+	Convulsions?	
None	6th grade	.....	8 years	None	+	+	+	+	+	+	+	+		
None	8th grade	.....	Lifetime	None	+	+	+	0	+	+	+	+		
None	2 years high school	.....	Lifetime	"Croup when baby"	+	+	+	0	+	+	+	+	.....	Stomach trouble

TABLE 2.—Clinical Chart of—

No.	Name	Hospital Number	Age	Race	Military Service	Active Duty	Symptoms Causing Patient to Fall Out	Occupation	Character of	Time Lost From Work
1	R. E.	1256	23	U. S.	3 months	1 week	Dizziness, weakness, precordial pain	Bell boy, chauffeur	Very ligth	About 2 months a year
2	F. A. C.	1285	24	U. S.	12 months	1 week	Weakness, precordial pain, blurred vision	Farmer	Moderate	1 to 2 months a year
3	W. P.	992	23	Italy	13 months	8 weeks	Precordial pain, dizziness, weakness	Teamster	Light	Day or two a month
4	F. P.	1067	29	Italy	4 months	1 week	Weakness, pain in back and legs	Fruit store	Light	About 1 week a month for years
5	G. W.	1423	22	U. S.	4½ months	1 month	Dyspnea and precordial pain	Farmer, coal miner	Heavy	Month out of each year
6	E. J. G.	1069	24	U. S.	4 months	3 weeks	Dyspnea and weakness	Clerk	Light	Very little
7	F. K.	711	25	Austrian Jew	4 months	5 days	Weakness, dizziness, nervousness	Furrier	Very light	4 or 5 months a year
8	W. Z.	873	25	U. S.	4 months	6 days	Fainted	Barber	Light	Worked 2 days a week
9	R. C.	874	24	U. S.	4½ months	1 week	Flat feet	Painter, traveling salesman	Light	2 to 3 days a week
10	G. D.	868	23	U. S.	3½ months	3 weeks	Dizziness	Department store clerk	Light	No work for 18 months
11	N. G.	1100	22	U. S.	17 months	11 months light duty	Dizziness	Salesman	Light	None
12	N. L.	1542	19	U. S.	14 months	2 days	Dyspnea and dizziness	Barber	Light	2 to 3 days a week
13	W. W.	1259	24	U. S.	3 months	3 weeks	Shortwinded, nervousness	Auto mechanic	Light	1 day in 2 weeks
14	T. P.	1228	22	U. S.	3 months	15 days	Dizziness and precordial pain	Drug clerk	Light	Practically none

prior to entrance into the army and were merely accentuated by the nervous and physical strain in the camps. This type of individual is frequently seen in civil life, where he is often classed as neurasthenic, and cannot be regarded strictly as a product of the war. They represent the group of patients with "irritable heart" whose symptoms have existed for a long time as contrasted to the cases whose symptoms are of short duration and date from some acute infection or nervous or physical strain. It is to the former group of patients particularly that attention is directed in the present paper. Incidental reference will be made to the epinephrin reaction in patients with "irritable heart" whose symptoms date from severe nervous or physical strain or from acute infections. No cases following "gassing" have been studied.

Those falling into the group with symptoms of long duration frequently date these symptoms back to childhood, and many state that they "inherited" them. In fact, it is the exceptional case in which the symptoms do not date back a number of years. They are usually the

—Epinephrin Negative Patients

Exercise	Education	Special Points of History	Duration of Symptoms	Alleged Etiology	Weakness	Dizziness	Blurred Vision	Fainting	Excitability	Nervousness	Dyspnea	Precordial Pain	Special Symptoms	Remarks
Active until 14 years	5th grade at 14 years	Always nervous	9 years	None	+	+	+	+	+	+	+	+		
Baseball but always dyspneic	5th grade at 16 years	Always weak	12 years	None	+	+	+	0	+	+	+	+	.....	"Knew he could not stand it when he joined"
Never because "short winded"	School 3 months	"Doctored a good deal"	Lifetime	None	+	+	+	0	+	+	+	+	.....	"Never felt good in his life"
None	None	Well until 10 years of age	19 years	Unknown illness	+	+	+	+	+	+	+	+	Pain in stomach, back and legs	
Active until 4 years ago	8th grade at 14 years	.....	2 years	None	+	+	+	+	+	+	+	0	Palpitation	
None	18 months high school	Easily tired	Lifetime	None	+	+	+	0	+	+	+	+	Palpitation at 14 yrs.	"Headaches and indigestion"
None	None	Always weak	Lifetime	None	+	+	+	+	+	+	+	+		
Walked half mile daily	6th grade at 18 years	.....	Lifetime	None	+	+	+	+	+	+	+	+	Incontinent at times	"Always weak and had dyspnea"
Athletic	3 years high school	.....	10 years	"Stomach trouble"	+	+	0	+	+	+	+	+	Palpitation	"Never strong since 14 yrs."
None	1 year high school	Always weak	Lifetime	"Born with it"	+	+	+	0	+	+	+	0	Throat trouble	
Athletic	Through high school	Always healthy	7 months	"Overwork"	+	+	+	0	0	+	+	+	Irritable	
None	5th grade	Always sickly	Lifetime	"Inherited"	+	+	+	+	+	+	+	+	Always nervous	
None	None	.....	Lifetime	"Inherited"	+	+	0	+	+	+	+	+		
None	8th grade	.....	Lifetime	None	+	+	+	+	+	+	+	+	.....	"Stomach trouble"

"delicate child"; they have been told in early life by the doctor that they had "heart trouble" and therefore must avoid any strain and all heavy work. As a result they have had to "favor" themselves. They were not allowed to play any of the more vigorous games, and if by chance they did try them, they had to give them up, for they soon found they could not keep pace with the other children. They got "short of breath"; they had "pain over the heart"; they felt weak and got tired. In school most of them had difficulties, as is shown in Tables 1 and 2, but this does not hold true for all of this group, for in exceptional cases they reached college.

As they grow older and the question of earning a livelihood confronts them they usually try several jobs or occupations, each successively lighter than the preceding one, until by the process of elimination they at last find one which can be adapted to themselves, and in which the work is so light that there is no strain and therefore their symptoms are less prominent. Nevertheless, their symptoms are easily

produced by exertion or nervous strain. Since their tendency is to "give in" easily to any discomfort, and to regard themselves as invalids it is quite characteristic for them to lose a considerable amount of time from their work. As a result of this their economic level is usually a low one. Such is their earlier life.

When called into the military service by the draft, or in a few cases by enlisting, they are brought face to face with a totally different existence. There is a considerable amount of physical exertion, and there is an element of nervous strain in it that to them looms very large. To succeed they must adapt themselves to these new conditions of life, for they can no longer adapt the conditions of life to their own personal limitations. They are started in light drill and immediately their symptoms begin to develop. As the severity of the drill is increased they begin to fall out, and when the hikes begin the active military careers of most of them come to an end. They fall out on account of "weakness," "dizziness," "pain over the heart," "shortness of breath," "palpitation," "blurring before the eyes," and quite often they faint. While many of the presenting symptoms suggest cardiac weakness, it is very striking that the most important underlying feature is often the tendency to general muscular fatigue. They complain of "being tired," and they give up to this feeling immediately. From Tables 1 and 2 it is interesting to note that when they arrive at the hospital, their actual military service may be measured in months, while their active duty is practically always measured in days or weeks. After the first few weeks their time is generally spent in the infirmaries or hospitals. The length of active duty of some of the cases in the tables deserves explanation. In Table 1, Cases 2, 8, 14, 19, 20 and 27, and in Table 2, Case 11, all did several months of active duty. In each of these cases active duty consisted of a few hours of light drill daily, and they were excused from all heavy drill and hikes. The active duty of Case 11 in Table 1, consisted of doing the work of a carpenter's assistant which he stated was very light work. The active duty of Case 19, Table 1, consisted of very light drill two or three times a week.

It will be noted in the tables that practically all of these men consider themselves "nervous" and easily excitable. A very striking fact was brought out on questioning them as to their reaction to gunfire. Twenty-eight of these men were questioned concerning their experiences on the rifle range. Eighteen patients stated that on going to the range during practice they began to tremble and "shake all over." The trembling often increased to such an extent that they had to give up practice. In two other instances officers noticed them shaking and sent them off the range. One fainted from excitement and had to be

sent to the hospital, and another collapsed and had to be carried from the range. Thus out of the twenty-eight questioned twenty-two, or 78.5 per cent. admitted that they could not stand gunfire. Two of the remaining six stated that they had never been within the sound of gunfire, and the other four stated that gunfire did not disturb them. Several admitted that they were afraid, while one stated that he was "scared to death." Others denied fear. The reaction to gunfire was about the same in the patients in Tables 1 and 2.

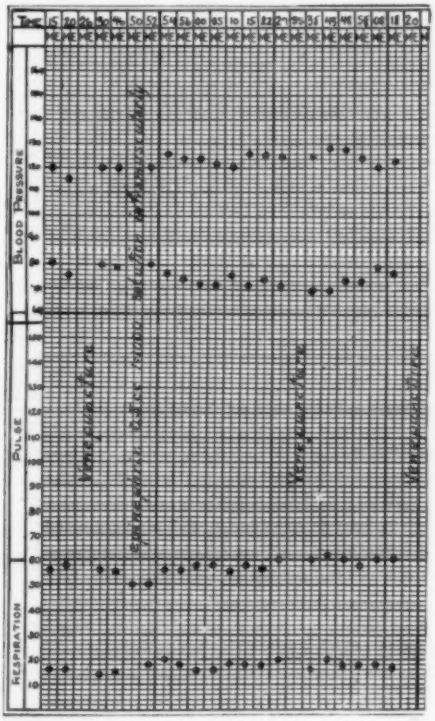

Chart 1.—Negative epinephrin reaction in a patient (F. B.) with mitral insufficiency. Venepuncture done twice during the observation period did not produce changes in the blood pressure, pulse or respiration.

Nervous hyperexcitability is also well illustrated in another way, and that is during the physical examination of the patients. When these men are examined by the ward surgeon the pulse rate is usually high, varying from 100 to 150 per minute. They may become flushed; they generally show a marked tremor of the hands and sometimes of both arms and legs; and they show increased sweating, most commonly

in the axilla and in the palms of the hands. They are quite apprehensive and the least noise startles them. If, however, they are allowed to lie quietly on the bed for an hour, all signs usually disappear. The pulse rate drops to normal, the tremor and sweating cease and they appear perfectly quiet. There are a few exceptions where a slight tremor or slightly increased pulse rate may persist. These

TABLE 3.—VERY SLIGHT TREMOR, PULSATION, QUESTIONABLE SWEATING, AND SLIGHT CHANGES IN THE TEMPERATURE OF THE HANDS PRESENT, BUT NOT ENOUGH TO INDICATE A POSITIVE REACTION

Time	Tremor	Sweating	Pulsations	Hands	Miscellaneous
9:10	Very slight	None	Very slight in neck	Warm	Quiet; no flushing or pallor
9:20	Very slight	None	Very slight in neck	Warm	Quiet; no flushing or pallor
9:26 Venepuncture					
9:30	Very slight	Very slight	Very slight in neck	Warm	Quiet; no flushing or pallor
9:46	Very slight	Very slight	Very slight in neck	Warm	Quiet; no flushing or pallor
9:50 Epinephrin 0.5 c.c. 1:1,000 solution intramuscularly					
9:52	+	Very slight	+	Warm	Quiet; no flushing or pallor
9:54	+	Very slight	+	Warm	Quiet; no flushing or pallor
9:56	+	±	±	Warm	Quiet; no flushing or pallor
10:00	+	±	±	Fingers sl. cool	Quiet; no flushing or pallor
10:05	±	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:10	+	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:15	+	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:22	±	±	+	Fingers warm	Quiet; no flushing or pallor
10:27	±	±	+	Fingers warm	Quiet; no flushing or pallor
10:35 Venepuncture					
10:38	±	None	+	Fingers warm	Quiet; no flushing or pallor
10:43	+	None	±	Fingers warm	Quiet; no flushing or pallor
10:48	+	None	±	Fingers warm	Quiet; no flushing or pallor
10:58	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:08	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:18	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:20 Venepuncture					

cases are in marked contrast to cases of hyperthyroidism whose pulse rate, tremor, etc., show only a slight decrease after an hour's rest. The physical examination of the heart usually shows a tachycardia, but otherwise nothing abnormal is made out.

We have injected epinephrin intramuscularly and made observations on seventy-three cases of the group of soldiers with "irritable heart" whose symptoms were of long standing. Of this number, forty-three, or 59 per cent., showed a definite hypersensitiveness to epinephrin

or gave a positive reaction as described above. Twenty-seven, or 37 per cent., showed no reaction. Three cases, or 4 per cent., gave a doubtful reaction.

The question naturally arises as to the difference between the cases showing positive and those showing negative reactions. After a careful clinical study of these two groups as charted in Tables 1 and 2 we have been unable thus far to find any differences, except that the reaction was more constant in those with pronounced neurotic tendencies.

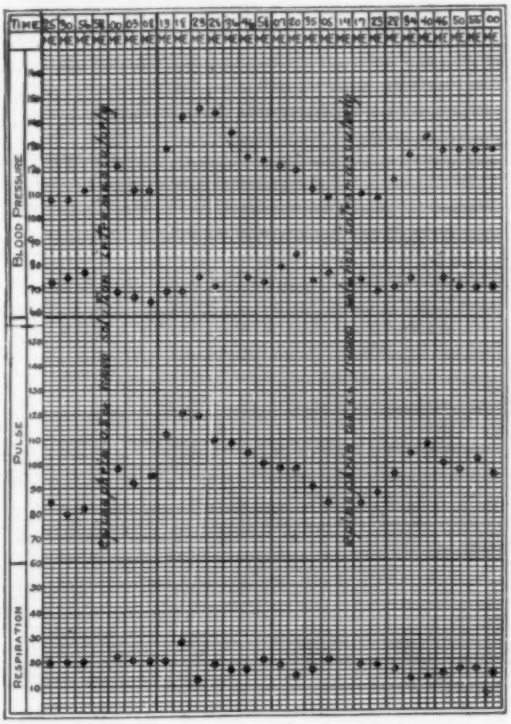

Chart 2.—Record of patient (A. W.) showing characteristic changes of a positive reaction following repeated doses at an interval of one hour.

As stated above, no claim is made that this whole group represents any single clinical entity, and it seems possible, though we have no proof to offer, that the positive and negative groups may have a different etiology for their symptoms.

This reaction to epinephrin is not peculiar to the group whose symptoms have existed for a considerable length of time. Observations have been made on eighteen cases of "irritable heart" in which the

TABLE 4.—Injection of 0.5 c.c. of Epinephrin Repeated at the End of an Hour in Patient with "Irritable Heart" whose Symptoms are of Long Duration *

Time	Tremor	Sweating	Flushing	Pulsations	Hands	Miscellaneous
12:05	+	0	+	Slight neck	Warm	Quiet
1:30	+	0	+	Slight neck	Warm	Quiet
1:56	+	+ palms	+	Neck, abdomen slight	Warm	Quiet
1:58 Epinephrin 0.5 c.c. of 1:1,000 solution intramuscularly						
2:00	++	+	Pale	Neck, abdomen	Cold	Pain over heart, breathing deep
2:03	++	+	More color	Neck, abdomen	Cold	Not such deep breathing
2:08	++	+	+	+	Warmer	Definite precordial pain, quiet
2:15	++	++	++	++	Cold	Coughing, pain, heart fast
2:20	+++	++	++	+++	Cold	Pain in precordium
2:34	+++	+	++	+++	Cold	Pain in precordium, quieter
2:52	++	+	+	++	Cold	Occasional pain, quieter
2:58	+	0	+	+	Cold	Quiet
3:08	Very sligth	+	+	+	Less cold	Quiet
3:20	Very sligth	+	+	+	Same	Quiet
3:35	Very slight	+	+	+ Slight neck	Warm	Quiet, reaction over
4:05	Very	+	+	+	Warm	Occasional extra systole
4:14 Epinephrin 0.5 c.c. of 1:1,000 solution intramuscularly						
4:17	+	+	+	+	Warm	Quiet, occasional extra systole
4:23	+	+	+	+	Warm	Quiet
4:28	+	+	+	+	Cooler	Restless
4:35	+	+	+	++	Cooler	Respiration very deep, restless
4:40	++	+	++	++	Cold	Respiration not so deep, restless
4:48	++	0	++	++	Cold	
4:45	++	0	++	++	Cold	Respiration not so deep, restless
5:00	+	0	++	++	Cold	Quiet
5:05	+	0	++	++	Cold	Quiet
5:10	+	0	++	++	Cold	Quiet
5:15	+	0	++	++	Cold	Quiet

* Following each injection there was the typical reaction of a hypersensitive individual, the second being somewhat less marked than the first.

symptoms dated to some recent infection, such as rheumatic fever or pneumonia, previous to which they had been able to do full duty. Of these, six gave positive reactions to epinephrin and twelve gave no reaction. Observations were also made on a group of cases in which symptoms developed following some nervous or physical strain. Of seven of this type, five gave a positive reaction and two gave no reaction. The proportion of positive reactions in cases of "irritable heart" is in distinct contrast to the complete absence of positive reactions among normal trained soldiers.

In our experience the epinephrin reaction, when present, remains remarkably constant in individuals with symptoms of "effort syndrome" of long standing. It would seem that when such an individual once shows a positive reaction he retains his hypersensitiveness for a considerable length of time.

To determine if the reaction varied in a given patient at different periods, the tests were repeated in thirty cases at intervals of time

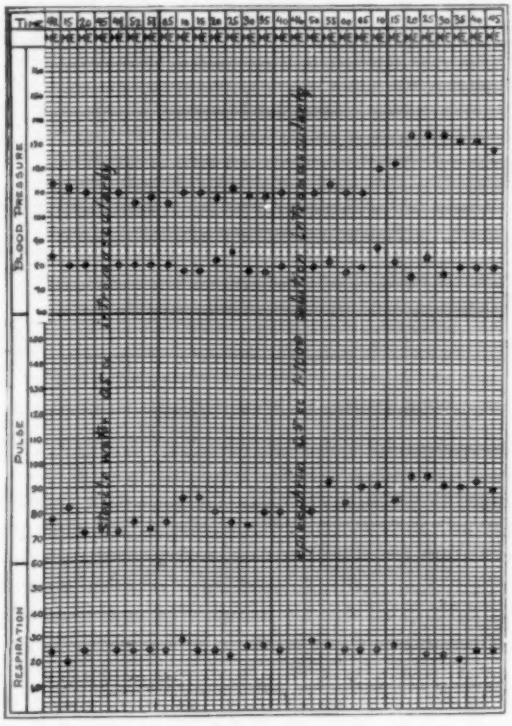

Chart 3.—Control test (A. M.) with the injection of 0.5 c.c. of sterile water intramuscularly without resultant change in the blood pressure, pulse or respiration. Observations were continued for one hour when 0.5 c.c. of a 1:1,000 solution of epinephrin was injected which produced a typical reaction.

varying between four and seventy-five days, the average being thirty days. Of nineteen cases which had previously given positive reactions, eighteen remained positive, while one case gave a doubtful reaction. In eleven epinephrin negative cases the reaction remained negative in nine, while in one it became positive and in another doubtful. In the case where the reaction changed from negative to positive the second reaction was obtained a few days after a tonsillectomy following which

the patient had complained of nervousness and possibly the operation could account for the increased sensitiveness. In a number of cases which gave reactions, the tests were repeated after the men had advanced several grades in the cardiac exercise classes, but this did not seem to affect the hypersensitiveness to epinephrin as the reaction remained positive.

TABLE 5.—No Change After Injection of 0.5 c.c. of Sterile Water. One Hour Later in the Same Patient 0.5 c.c. of 1:1,000 Solution of Epinephrin Produced the Characteristic Picture of a Positive Reaction with Tremor, Flushing, Pulsation and Palpitation

Time	Tremor	Sweating	Flushing	Pulsations	Miscellaneous
2:20	+?	0	0	0	Quiet
2:30	Suggestive	0	0	+	Quiet
2:45 H_2O 0.5 c.c. intramuscularly					
2:48	+?	0	0	+	Quiet
2:52	0	0	0	+	Quiet
2:58	0	0	0	+	Quiet
3:05	+?	0	0	+	Quiet
3:20	0	0	0	+	Quiet
3:40	+?	0	0	+	Quiet
3:46 Epinephrin 0.5 c.c. of 1:1,000 solution intramuscularly					
3:55	+	0	0	+	Quiet
4:05	++	0	0	+	Quiet
4:15	++	0	0	++	Quiet
4:25	++	0	+	Head, neck, +++ abd.	"Heart thumping away"
4:35	++	0	+	+++	
4:40	++	0	+	++	Not so much throbbing
4:45	++	0	+	+	Quiet

On entrance to this hospital all of the patients had routine strength tests as done on the cardiovascular service.[6] The strength to weight ratio of the epinephrin positive patients was 17.4; that of the epinephrin negative patients was 16.8. Thus, there is practically no difference in the muscular strength of the two groups. Though some of the patients showed a measurable increase in strength, in general, they were not the type that progressed well in the exercises. Indeed, not one of the epinephrin negative men returned to full duty, and it will be seen from the table that the disposition of the positive and negative groups was about the same.

DISPOSITION OF SEVENTY-ONE CASES OF "IRRITABLE HEART" WITH SYMPTOMS OF LONG STANDING

Disposition	Epinephrin Positive Number	Epinephrin Positive Per cent.	Epinephrin Negative Number	Epinephrin Negative Per cent.
Domestic service	16	36.3	9	33.3
Cert. of disability	28	63.7	15	55.6
Full duty			3	11.

6. Smith, Bertnard: The Possibilities of Physical Development in Cases of Effort Syndrome by Means of Graded Exercises. Arch. Int. Med., this issue, p. 321.

In order to determine if the cases which gave a negative reaction with a small dose of epinephrin would react positively to a larger amount, ten men who had previously been classified as negative were given 1 c.c. of a 1:1,000 solution of epinephrin intramuscularly. In five of these cases there were no changes of importance following the increased dose, but in the five remaining cases there was a slight increase in pulse rate and blood pressure rise, varying between 10 and

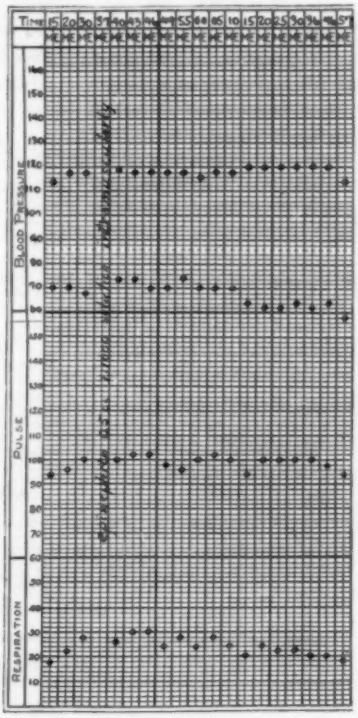

Chart 4.—Negative reaction in a patient (F. C.) with "irritable heart" whose symptoms date back for twelve years (Case 2 of the clinical chart of epinephrin negative patients). There is nothing to indicate even the slightest reaction to epinephrin.

20 mm. Also in some there was slight tremor and pulsation, but no restlessness or complaints of nervousness, precordial pain, etc. The picture was that of the reaction of a normal individual to a moderately large dose of epinephrin rather than that of a true hypersensitiveness to the drug. It would seem from these observations that the dose of 0.5 c.c. of a 1:1,000 solution of epinephrin is sufficient to produce all

the symptoms necessary to recognize a hypersensitiveness, while 1 c.c. of a 1:1,000 solution may produce moderate changes in a normal person.

SUMMARY

The reaction to the intramuscular injection of a small dose (0.5 c.c. of a 1:1,000 solution) of epinephrin, has been studied in normal soldiers, and in a group of soldiers showing symptoms of so-called "irritable heart." Of twenty-six normal soldiers, who had gone through the grill of army training in its severest form for fourteen months, not one gave a positive reaction as judged by observation of pulse rate, blood pressure, objective signs or subjective symptoms.

TABLE 6.—SLIGHT CHANGES FOLLOWING THE INJECTION OF EPINEPHRIN, BUT NOT ENOUGH TO INDICATE A POSITIVE REACTION

Time	Tremor	Sweating	Flushing	Pulsations	Miscellaneous
2:15	.....	.....	.....	Slight neck	Quiet; no pulsation in fingers, not cold
2:25	Very slight	.....	.....	Slight neck	Quiet
2:30	Very slight	.....	.....	Sligth neck	Quiet
2:37 Epinephrin 0.5 c.c. of 1:1,000 solution intramuscularly					
2:40	Very slight	.....	.....	Slight neck	Quiet
2:43	Very slight	.....	.....	Slight neck	Quiet
2:46	Very slight	.....	.....	Slight neck	Quiet
2:49	Very slight	.....	.....	Slight neck	Quiet
2:55	Very slight	.....	.....	Slight neck	Quiet
3:00	Very slight	.....	.....	Slight neck	Quiet
3:05	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:10	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:15	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:20	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:25	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:30	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:35	Sligth increase	Slight	.....	Slight neck	Slightly uneasy
3:46	Slight increase	Slight	.....	Slight neck	Slightly uneasy
3:56	Slight increase	Slight	.....	Slight neck	Slightly uneasy

Seventy-three patients with symptoms of "irritable heart" were studied. Their symptoms were of long duration and for the most part antedated their entrance into military life. Of this group about 60 per cent. gave a reaction which definitely indicated a hypersensitiveness to epinephrin. We know that epinephrin has a selective action on the sympathetic autonomic nervous system. One may, therefore, naturally suggest that the symptoms and signs induced in the positive cases are the result of a hypersensitive sympathetic autonomic nervous system. A careful clinical analysis, however, of the patients showing positive and negative reactions has revealed no essential clinical differences

between the two groups. One cannot state that the clinical condition of the patients who are sensitive to epinephrin depends in any way directly on the factors underlying the positive reaction. On the other hand, this is not at all impossible, and there is nothing to lead one to conclude that the factors causing the symptoms in the positive and negative groups are the same. It appears to be certain, however, that this group of patients is not good material from which to make a soldier.

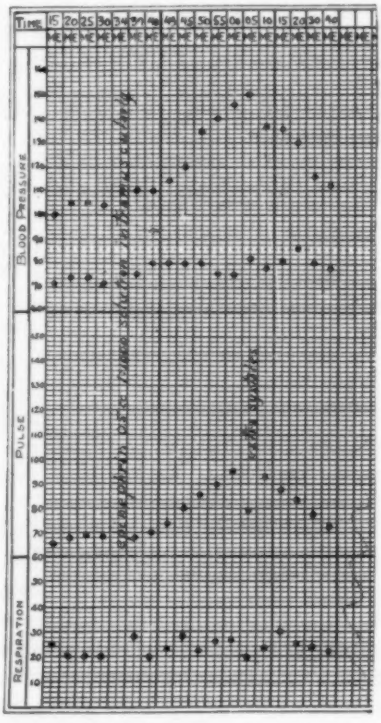

Chart 5.—A definitely positive reaction in an individual (D. C.) with long-standing symptoms of "irritable heart." There is a characteristic sharp rise in systolic blood pressure after a period of nine minutes, with a slight fall in the diastolic blood pressure at the height of the reaction. Associated with the blood pressure changes there is an increase in the pulse from 68 to 94, and the extrasystoles which were present before the administration of the epinephrin, become very numerous.

Although all efforts were made to improve the physical condition of these men, not one of those who gave a positive reaction, and only three who gave negative reactions were able to go to full duty. They

were unable to stand the strain and in addition their reaction to gunfire makes them all the more undesirable for full duty. They are not fit to fight, and even in limited service their value is questionable. This class of patients is not a true product of the war, for they are seen

TABLE 7.—Marked Tremor Which Became Generalized, Flushing, Marked Pulsation, Restlessness and Precordial Pain Indicating Positive Reaction (D. C.)

Time	Tremor	Sweating	Flushing	Pulsation	Miscellaneous
8:10	++ coarse	+ palms moist	None	+ in neck	Rather restless, occasional extra systoles
9:20	++ arm tremor	+ palms moist	None	+ in neck	Numerous extra systoles
9:25	++ arm and hand coarse	+ palms moist	None	+ in neck	Rather restless, extra systoles same
9:30	++ arm and hand coarse	+ palms moist	None	+ in neck	Rather restless, extra systoles same
9:34*					
9:37	+++ arm trembling	+ palms moist	+	+ in neck	Chin trembling, restless
9:40	+++	+ palms moist	+	+ in neck	Respirations deep, extra systoles same
9:43	+++ coarse	+ palms moist	+	+ in neck	
9:45	+++ coarse	+ palms moist	++	++ in neck	Respirations not so deep
9:50	+++ whole arm	+ less	++	++ in neck	Restless, neck muscles trembling
9:55	+++ trembling all over	+ less	++	+++	Precordial pain, neck and arms trembling
10:05	+++	+ same	++	++	Numerous extra systoles
10:10	++	+	++	++	Numerous extra systoles
10:15	++	+	++	++	Numerous extra systoles
10:20	++	+	++	++	Not so restless
10:32	++	+	++	+	More quiet
10:42	++	+	+	+	Quiet

* Epinephrin 0.5 c.c. 1:1,000 solution intramuscularly.

not only in military but also in civilian life. They are of the type who go from one outpatient clinic to another with complaints of nervousness, weakness, palpitation, precordial pain and dyspnea. They are classed as neurotic or neurasthenic individuals and have usually been receiving medical attention for years. As a class they have assumed a new importance since their induction into the army. There seems to be a certain level of strain below which these people can live without their symptoms, and their one effort in life is to keep below this level. Above it their symptoms appear and they break. This explains why they are found in the army as a class and not in civil life as such. In both places, however, they present a problem of no little importance to the internist and to the practitioner of general medicine.

We are glad to take this opportunity to express our thanks to Miss Edna H. Tompkins for her constant assistance in making many of the observations on which this study has been based.

STUDIES ON EPINEPHRIN. II

THE EFFECTS OF EPINEPHRIN ON THE BASAL METABOLISM IN SOLDIERS WITH "IRRITABLE HEART," IN HYPERTHYROIDISM AND IN NORMAL MEN *

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INTRODUCTION

During a general course of study on the syndrome of the so-called "irritable heart of soldiers," investigation was made into the frequently alleged relationship of this disorder to hyperthyroidism. Among other methods of examination employed in the study was the epinephrin reaction as used by Goetsch.[1] He reports that patients with hyperthyroidism are hypersensitive to epinephrin in that following the injection of the drug a much greater response is obtained than is the case in normal individuals. This response consists in a rise of blood-pressure and pulse rate, and the production of certain characteristic symptoms.

In the investigation at General Hospital No. 9 on patients showing the symptom complex of the "irritable heart of soldiers," it has been found that a considerable percentage of these cases are also hypersensitive to the drug. Careful clinical analysis, however, as well as determinations of the basal metabolism, do not lend any support to the theory that hyperthyroidism is an underlying feature in the condition. It was hoped, therefore, that a study of the basal metabolism under the effects of epinephrin would assist in the explanation not only of why there was a response to the drug in any of the cases of "irritable heart," but further as to why this response was evoked in only a certain percentage of the cases. Incidentally, the opportunity to study

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* This investigation was suggested by and started under the direction of Major Francis W. Peabody, M. C., U. S. Army, and completed under the direction of Capt. Bertnard Smith, M. C., U. S. Army, at U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Goetsch, E.: Newer Methods in the Diagnosis of Thyroid Disorders: Pathological and Clinical, N. Y. State J. M. **18**:259 (July) 1918.

the effects of epinephrin on subjects in whom no unusual reaction was produced by the drug and also on a group of cases who were hypersensitive to it, promised to throw some light on the physiological effect of epinephrin in the organism.

REVIEW OF THE LITERATURE

Most studies of the respiratory exchange under the effects of epinephrin have been made more from interest in the resulting carbohydrate mobilization and combustion as illustrated by changes in the respiratory quotient than in the effect on the total metabolism. It is this viewpoint, probably, together with the unsatisfactory valuation to be placed on respiratory quotient figures, which accounts for the few studies concerning the influence of epinephrin on the heat production.

The results of animal experimentation upon the question show absolute disagreement. According to Hari,[2] Welecki found the carbon dioxid and water output lowered after intraperitoneal injection of epinephrin and elevated after intravenous injection. Hari, using curarized animals, found a diminished metabolism under both conditions of injection, although an elevated respiratory quotient. Jackson[3] also reported diminished oxygen intake. Wilenko,[4] working on animals under urethane, found no change in metabolism or respiratory quotient after epinephrin, but at the same time a total absence of the normal rise in both factors on simultaneous carbohydrate feeding. On the other hand, La Franka[5] and Bernstein[6] obtained elevation in the oxygen intake but unchanged quotients, while Lusk[7] showed increase in the respiratory quotient as well as in the metabolism.

The clinical studies, while consistent, are too few in number to allow definite conclusions to be drawn as to the effects of epinephrin on heat output. The reports of both Fuchs and Roth,[8] and of Bern-

2. Hari, P.: Ueber den Einfluss des Adrenalins auf den Gaswechsel, Biochem. Ztschr. **38**:23, 1912.

3. Jackson, D. E.: An Experimental Investigation of Certain Phenomena Relating to the Action of Drugs on the Rate of Oxygen Consumption in the Animal Body, J. Lab. & Clin. M. **2**:145 (Dec.) 1916.

4. Wilenko, G. G.: Ueber den Einfluss des Adrenalins auf den Respiratorischen Quotienten und die Wirkungeweise des Adrenalins, Biochem. Ztschr. **42**: 44, 1912.

5. La Franka, S.: Untersuchen über den Respiratorischen Stoffwechsel bei Experimenteller Glycosuria, Ztschr. f. Exper. Path. u. Therap. **6**:1, 1909.

6. Bernstein, S.: Studien über die Wirkung einzelner Blutdruesen Extrakte in besonders auf den Respratorischen Stoffwechsel, Ztschr. f. Exper. Path. u. Therap. **15**:86, 1914.

7. Lusk, G.: Animal Calorimetry. VIII. The Alleged Influence of the Adrenals on Diabetic Metabolism, Arch. Int. Med. **13**:673 (April) 1914.

8. Fuchs, D., and Roth, N.: Untersuchungen über die Wirkung des Adrenalins auf den Respiratorischen Stoffwechsel, Ztschr. f. Exper. Path. u. Therap. **10**:187, 1912.

stein and Falta[9] show a decided rise in caloric production and in respiratory quotient on subcutaneous injection of one milligram of epinephrin; but these reports are in total on but seven cases, and those of different types. They are on two cases of acromegaly, one of Addison's disease, one infant and three normal men. They show no distinction between the normal and the pathologic cases.

METHODS

Due to this deficiency in clinical data we felt it necessary to study not only the cases of "irritable heart," but a group of normal cases for comparison. For this purpose men with simple organic heart lesions as well as the admittedly normal man seemed a most satisfactory contrast to the "irritable heart" group. Patients with hyperthyroidism, on the other hand, presented the best pathologic contrast.

With the exception of the preliminary rest period, the epinephrin test was conducted essentially along the lines stipulated by Goetsch. Our patients rested in bed for but one to two hours before the test was started. The pulse, blood pressure and respiration readings, together with records of the objective state of the patient — tremor, vasomotor reactions, pulsations — were charted from time to time during this rest period until the records showed a constant level. There was then injected into the deltoid muscle 0.5 c.c. of 1:1,000 "adrenalin" solution, freshly prepared from the tablets as put up by Parke, Davis and Company. The chart readings were then taken every three minutes for several readings, then every five minutes until the end of an hour, and then every ten minutes for one-half hour longer.

A typical response to the injection consists in a rise in systolic blood pressure of at least 10 mm. of mercury, with a concomitant acceleration in pulse rate of at least 10 beats per minute. The diastolic blood pressure may rise, fall or remain unaltered. Parallel with these changes is an increase in certain characteristic signs and symptoms — tremor, vasomotor reactions, palpitation and at times precordial pain. Such, then, are the criteria for the minimum changes that a reaction to the drug must fulfil in order that it may be called "positive" and the patient be considered "epinephrin sensitive."

When these changes are not produced in this characteristic combination and degree, the reaction is regarded as "negative."

Between this group of patients with definitely positive or negative reactions a small number were met with who had to be classified as "questionable reactions."

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9. Bernstein, S., and Falta, W.: Ueber die Einwirkung von Adrenalin, Pituitrinum Infundibulare, und Pituitrinum Glandulare auf den Respiratorischen Stoffwechsel, Verhandl. d. Deutsch. Kongresses f. Inn. Med., Wiesbaden, 1912.

As is described in detail in the general report on the effects of epinephrin in a separate paper,[10] the time interval between the injection and reaction, and the grade and duration of the latter showed variations; but for the purposes of this report it is unnecessary to distinguish further than between positive and negative reactions.

The metabolism was determined by the Tissot method. A 100 liter spirometer was used in connection with a half mask covering nose and mouth. The analyses of the expired air were made on the portable Haldane gas analysis apparatus. Values for the respiratory rate and depth were based on pneumographic records of the respiration. All volumes were computed in the standard way. The calorific production was obtained by indirect calorimetry as the method implies. It was computed from the nonprotein respiratory quotient. Nitrogen analyses were not made. The heat production per square meter of body surface was based on the height-weight formula of DuBois,[11] and the standards of metabolism for varying ages as established by DuBois and associates.

All periods were from nine to ten minutes in duration with the exception of rare instances when the spirometer was filled too rapidly to permit of so long a period. All patients had been fasting from twelve to fourteen hours. All received two independent basal determinations as a base line for later changes in metabolism.

The first basal period was obtained after the patient had been at rest until the pulse showed a constant level. The second basal determination was made with a new placement of the mask, and after the performance of any disturbing factors which the requirements of the complete study would later necessitate. These included blood pressure readings, venepuncture for blood sugar analyses, blood smears and electrocardiographic studies. We, therefore, feel that two agreeing basal periods under these conditions assure not only a satisfactory base line from which to judge later metabolic changes, but also assure that such metabolic changes are due to the epinephrin and not to other factors.

If a metabolic determination was to be started within five minutes of the epinephrin injection, the mask was not removed after the second basal period. Also it was not removed when periods started within fifteen minutes of each other. Otherwise, it was replaced for all periods.

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10. Wearn, J. T., and Sturgis, C. C.: Effects of the Injection of Epinephrin in Soldiers with "Irritable Heart." Arch. Int. Med., this issue, p. 247.

11. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known, Arch. Int. Med. **17**: 863 (June) 1916.

12. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

The beginning of metabolism periods subsequent to the injection depended largely upon the patient's response to the drug. In cases that gave a positive reaction, the metabolism was determined as nearly as possible at the height of the reaction, as well as at some time before and after this point. In the negative cases any index of metabolic disturbance was, of course, lacking. Determinations were thus made on a time comparison with the positive cases — about thirty minutes after the injection. Here, also, they were made at various times before and after that.

PRESENTATION OF DATA

Four groups of subjects have been studied. Two of these groups were "epinephrin negative" and showed no reaction, while two were "epinephrin positive" and responded with the typical reaction of the hypersensitive subject. The "epinephrin negative" groups consisted of normal subjects, and of patients with "effort syndrome" who did not react to epinephrin. The "epinephrin positive" groups consisted of patients with "effort syndrome" who reacted to epinephrin and a small series of cases of hyperthyroidism. Tables 1, 2, 3 and 4 give simply the hospital records and detailed metabolic data of these groups. Tables 5, 6, 7 and 8 tabulate the salient metabolic findings in relation to epinephrin reaction. In these tables, only the average values of the two basal periods have been given. They are represented by periods 1 and 2. Our limit for satisfactory agreement in the percentage normality of the metabolism in two basal periods is a variation of 3 per cent. Any cases showing a greater disagreement than this are starred. Of these, none disagree by more than 6 per cent.

The pulse and blood pressure readings are the average values charted over the duration of the metabolic determination, nine minutes. The presence of subjective symptoms more intense than in the basal determinations is noted by a plus sign.

DISCUSSION OF RESULTS

With unbroken regularity the metabolism shows a rise after the injection of epinephrin. This is true in the normal as well as in the pathological cases. It is true whether there is any other sign of reaction or not. This increase in metabolism, however, is far more marked in those cases with a positive than in those with a negative reaction. With but one exception (Case 7, Table 1) every positive reaction was accompanied by a rise in metabolism of 20 per cent. or over. On the other hand, no negative reaction shows a rise above 20 per cent., and on the whole not above 15 per cent.

TABLE 1.—METABOLISM DETERMINATIONS ON "EPINEPHRIN POSITIVE" PATIENTS WITH "IRRITABLE HEART"

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism									
								Period No.	Minutes from Injection to Period Start	CO_2 per Min. C.c.	O_2 per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Volume per Respiration, C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
1	G. A.	729	Aug. 27	24	174	68.2	97.4	1-2	...	203	254	0.81	78	15.6	5.47	348	40.1	+ 2
								3	2	236	276	0.85	103	17.5	6.48	370	44.0	+11
								4	41	251	332	0.75	124	17.4	7.09	408	51.7	+31
								5	96	195	252	0.77	90	19.9	6.10	306	39.4	± 0
2	F. B.	1146	Aug. 24	31	181	70.1	98.3	1-2	...	218	266	0.82	75	17.9	6.45	361	38.7	− 3
								3	10	257	297	0.86	84	16.7	7.11	425	43.7	+11
								4	30	311	339	0.92	108	19.3	8.57	445	50.7	+28
3	H. B.	1143	Sept. 4	20	170	57.7	98.2	1-2	...	184	237	0.78	59	17.6	5.38	306	40.6	+ 3
								3	3	214	241	0.89	66	17.8	6.12	343	42.5	+ 8
								4	29	225	287	0.78	71	19.5	6.86	392	49.2	+25
								5	87	192	254	0.75	66	14.7	5.49	373	43.3	+10
4	D. C.	2395	Aug. 30	26	177	63.0	97.8	1-2	...	231	272	0.85	68	16.9	6.15	365	44.6	+18
								3	3	252	291	0.87	73	19.7	6.66	337	47.9	+21
								4	51	275	335	0.82	85	18.3	7.75	424	54.6	+38
5*	F. E.	2581	Sept. 23	21	165	56.8	97.4	1-2	...	135	193	0.71	72	13.0	3.59	276	33.4	−16
								3	29	178	251	0.71	87	15.5	4.92	318	43.4	+10
6	J. F.	423	Sept. 3	23	172	58.2	....	1-2	...	184	227	0.81	71	21.7	6.25	289	38.9	− 2
								3	2	207	242	0.85	71	21.4	6.71	314	42.1	+ 7
								4	26	268	290	0 92	90	24.3	9 08	374	51.2	+30
								5	88	217	250	0.87	72	22.1	7.74	350	43.6	+10
7	W. H.	984	Aug. 9	30	167	51.4	98.5	1-2	...	164	189	0.87	60	14.8	4.45	301	35.3	−11
								3	18	202	214	0.94	74	16.7	5.62	336	40.6	+ 3
								4	33	200	219	0.91	73	17.8	5.76	324	41.4	+ 5
								5	74	132	184	0.71	65	16.0	3.99	249	33.0	−16
8	K. K.	1226	Aug. 29	23	173	61.9	....	1-2	...	180	232	0.78	97	14.5	4.92	341	38.2	− 4
								3	1	243	256	0.95	123	18.8	6.91	367	44.0	+11
								4	35	180	288	0.63	124	18.1	5.78	319	46.5	+18
9	F. K.	1097	Aug. 10	36	171	58.9	....	1-2	...	178	220	0.81	73	21.5	5.77	268	37.6	− 5
								3	19	216	260	0.83	92	21.6	6.70	310	44.7	+13
								4	36	213	269	0.79	90	21.3	6.68	314	45.7	+16
								5	94	196	254	0.76	84	22.2	6.19	279	42.8	+ 8
								6	110	190	245	0.78	82	21.2	5.97	282	41.5	+ 5
10*	J. K.	1177	Aug. 17	31	166	59.8	....	1-2	...	181	236	0.77	64	23.5	5.72	244	40.4	+ 2
								3	20	237	294	0.81	75	21.3	7.08	333	50.8	+29
								4	65	185	255	0.73	76	20.0	5.69	284	43.3	+10
11	E. McC.	707	Aug. 13	20	172	63.6	98.2	1-2	...	175	213	0.82	...	12.9	4.62	360	35.1	−12
								3	10	197	242	0.81	...	14.1	5.07	359	39.8	+ 1
								4	33	218	269	0.81	...	15.7	5.83	371	44.2	+12
								5	78	186	197	0.94	...	11.0	4.81	435	33.3	−16
12*	J. S.	870	Aug. 22	24	164	60.1	....	1-2	...	286	266	1.08	79	15.4	9.27	600	45.8	+16
								3	10	263	284	0.93	76	15.9	8.90	559	48.0	+22
								4	34	302	336	0.90	100	18.9	9.93	524	56.3	+43
								5	67	321	300	1.07	84	16.2	10.27	633	51.6	+31
13*	F. S.	721	Aug. 19	23	173	63.4	98.8	1-2	...	235	285	0.83	65	45.7	10.80	237	46.6	+18
								3	21	271	335	0.81	75	58.3	14.56	250	54.7	+38
								4	55	263	324	0.81	68	63.8	15.22	238	52.9	+34
								5	83	236	286	0.82	72	58.7	14.74	251	46.8	+18

TABLE 2.—METABOLISM DETERMINATIONS ON "EPINEPHRIN POSITIVE" PATIENTS WITH HYPERTHYROIDISM

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Period Start	CO_2 per Min. C.c.	O_2 per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Volume per Respiration, C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
32	R. J.	2410	Aug. 6	27	166	50.0	99.0	1–2	...	256	344	0.75	...	19.8	7.66	388	63.4	+61
								3	10	313	380	0.83	133	21.3	9.21	432	71.6	+81
								4	26	290	380	0.76	134	21.3	8.94	420	70.3	+78
33	T. M.	851	Aug. 16	19	173	64.3	....	1–2	...	280	358	0.80	94	18.0	7.22	402	58.2	+42
								3	12	365	425	0.86	120	18.2	9.12	501	70.2	+71
								4	41	365	424	0.86	122	19.5	9.61	492	70.0	+71
								5	91	331	397	0.83	119	17.9	8.70	487	65.2	+59
34	E. S.	896	Oct. 25	27	185	72.5	99.2	1–2	...	284	364	0.78	109	19.1	8.46	444	53.4	+35
								3	6	422	440	0.96	130	18.6	11.68	628	67.7	+71
								4	31	333	428	0.78	137	18.1	9.99	553	62.8	+59

TABLE 3.—METABOLISM DETERMINATIONS ON "EPINEPHRIN NEGATIVE" PATIENTS WITH "IRRITABLE HEART"

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism									
								Period No.	Minutes from Injection to Period Start	CO_2 per Min. C.c.	O_2 per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Volume per Respiration C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
14	N. A.	2327	Nov. 7	32	183	72.3	97.6	1-2	...	242	278	0.87	58	17.5	7.50	429	42.0	+ 7
								3	5	258	290	0.86	65	17.6	7.90	449	45.1	+14
								4	32	263	330	0.82	64	19.6	8.55	436	47.7	+21
15	A. C.	2194	Oct. 24	25	177	60.5	....	1-2	...	231	274	0.85	84	16.0	6.44	404	45.7	+16
								3	5	239	288	0.90	89	18.1	7.44	411	48.6	+23
								4	31	247	285	0.86	90	19.0	7.49	394	47.7	+21
16*	F. C.	2171	Oct. 31	25	166	56.4	98.2	1-2	...	188	242	0.78	74	6.5	4.28	657	42.8	+ 9
								3	5	206	251	0.82	77	8.5	4.91	575	44.9	+14
								4	35	205	267	0.77	77	7.3	4.83	663	47.2	+19
17	E. G.	1069	Oct. 7	24	165	55.5	98.7	1-2	...	158	204	0.77	74	11.0	4.18	380	35.9	— 9
								3	18	184	225	0.82	89	9.9	4.70	476	40.1	+ 2
18	L. J.	1028	Aug. 23	23	174	65.0	....	1	...	186	226	0.82	72	17.7	5.08	288	36.7	— 7
								2	8	200	248	0.81	71	18.9	5.61	297	40.3	+ 2
								3	40	187	247	0.76	76	19.1	5.57	292	39.5	± 0
								4	76	179	235	0.76	70	18.1	5.04	279	37.6	— 5
19	J. L.	2484	Aug. 7	29	168	64.1	98.2	1-2	...	208	256	0.81	69	28.8	6.91	222	42.5	+ 8
								3	15	251	289	0.87	71	30.3	8.70	240	48.7	+23
								4	31	252	291	0.87	75	28.1	9.08	287	49.0	+24
20	R. L.	1971	Nov. 4	23	175	61.1	....	1-2	...	181	231	0.78	69	10.1	4.31	430	37.8	— 5
								3	5	190	233	0.81	73	10.7	4.33	405	38.5	— 3
								4	34	192	247	0.77	72	11.1	46.9	422	40.4	+ 2
21	M. H.	1104	Aug. 8	23	168	63.4	98.4	1-2	...	170	216	0.79	61	24.8	5.66	229	35.7	—10
								3	22	200	236	0.85	71	22.8	6.42	281	39.5	± 0
								4	39	151	188	0.80	70	23.1	4.83	209	31.1	—21
22	O. N.	1243	Oct. 19	29	166	60.2	98.8	1-2	...	204	250	0.82	72	18.0	6.00	334	43.3	+10
								3	33	211	268	0.79	80	18.8	6.21	330	46.1	+17
23	M. T.	2920	Jan. 24	25	172	63.2	97.4	1-2	...	178	222	0.80	52	....	4.82	...	36.6	— 8
								3	16	227	262	0.87	58	....	5.79	...	43.9	+11
								4	31	190	243	0.78	64	....	4.79	...	39.8	+ 1
24	I. Z.	1230	Aug. 21	22	177	60.2	....	1-2	...	187	232	0.81	72	12.8	4.38	342	38.4	— 3
								3	5	209	248	0.84	71	12.8	5.15	372	41.4	+ 5
								4	39	205	248	0.83	72	14.4	5.49	381	41.3	+ 5
25	D. Z.	2195	Nov. 1	22	191	73.0	98.2	1-2	...	257	308	0.85	71	18.3	7.23	396	44.2	+12
								3	5	273	312	0.87	71	20.0	7.34	362	45.7	+16
								4	35	277	329	0.84	70	20.5	7.85	382	47.9	+21

TABLE 4.—Metabolism Determinations on "Epinephrin Negative" Patients—All Normal Men

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Period Start	CO_2 per Min. C.c.	O_2 per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Volume per Respiration, C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
26	F. B.	1244	Oct. 3	29	183	84.1	....	1–2	...	225	272	0.87	56	13.9	5.79	476	38.6	− 3
								3	31	267	293	0.91	58	10.4	6.97	426	42.2	+ 7
27	G. F.	2241	Oct. 30	20	168	62.7	98.8	1–2	...	211	241	0.87	74	16.7	5.43	324	41.3	+ 5
								3	4	229	241	0.95	75	17.5	6.02	345	42.2	+ 7
								4	34	233	257	0.91	82	17.9	6.17	346	44.5	+13
28*	W. J.	813	Sept. 9	24	174	64.5	....	1–2	...	202	248	0.82	63	9.6	4.98	521	40.3	+ 2
								3	3	222	250	0.89	64	14.3	5.91	412	41.4	+ 5
								4	39	215	275	0.78	63	10.9	5.80	534	44.3	+12
								5	96	200	235	0.85	71	9.6	5.22	543	38.5	− 3
29	J. K.	1618	Sept. 6	23	180	68.6	97.6	1–2	...	170	224	0.77	66	12.0	4.67	389	34.2	−14
								3	2	181	229	0.79	70	12.0	4.98	415	35.2	−11
								4	37	191	252	0.76	69	12.1	5.20	430	38.5	− 3
								5	84	149	219	0.68	66	11.0	4.06	371	32.9	−17
30	R. L.	2556	Oct. 18	18	183	80.0	99.2	1–2	...	264	328	0.81	77	22.8	7.58	333	46.6	+14
								3	36	273	349	0.78	75	23.1	7.04	305	49.2	+20
31	J. R.	2160	Nov. 16	33	176	66.6	98.2	1–2	...	231	280	0.83	71	11.1	6.31	568	44.6	+13
								3	3	256	296	0.87	66	11.3	7.00	621	47.7	+21
								4	34	225	298	0.75	65	11.5	6.19	541	46.6	+18

The two basal periods disagreed between 3 and 6 per cent.

TABLE 5.—Correlation of Metabolic and Reaction Data on "Epinephrin Positive" Patients with "Irritable Heart"

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
1	1-2	..	+ 2	....	0.81	78	15.6	5.47	109	85	
G. A.	3	2	+11	+ 9	0.85	108	17.5	6.48	116	85	+
	4	41	+31	+29	0.75	124	17.4	7.09	144	100	++
	5	96	+ 0	— 2	0.77	90	19.9	6.10	110	94	
2	1-2	..	— 3	....	0.82	75	17.9	6.45	118	80	
F. B.	3	10	+11	+14	0.86	84	16.7	7.11	120	79	+
	4	50	+28	+31	0.92	108	19.2	8.57	143	88	++
3	1-2	..	+ 3	....	0.78	50	17.6	5.38	97	66	
H. B.	3	3	+ 8	+ 5	0.89	66	17.8	6.12	105	69	+
	4	39	+25	+22	0.78	71	19.5	6.86	114	64	+
	5	87	+10	+ 7	0.75	66	14.7	5.49	96	60	
4	1-2	..	+13	....	0.85	68	16.9	6.15	104	74	
D. C.	3	3	+21	+ 8	0.87	73	19.7	6.66	113	78	++
	4	31	+38	+25	0.82	85	18.3	7.75	143	79	++
5	1-2	..	—16	....	0.71	72	13.0	3.50	109	80	
F. E.	3	29	+10	+26	0.71	87	15.5	4.92	125	78	+
6	1-2	..	— 2	....	0.81	71	21.7	6.25	126	90	
J. F.	3	2	+ 7	+ 9	0.85	71	21.4	6.71	129	94	
	4	26	+30	+32	0.92	90	24.3	9.08	155	97	+
	5	88	+10	+12	0.87	72	22.1	7.74	129	90	
7	1-2	..	—11	....	0.87	60	14.8	4.45	100	75	
W. H.	3	18	+ 3	+14	0.94	74	16.7	5.62	113	79	+
	4	33	+ 5	+16	0.91	73	17.8	5.76	119	82	++
	5	74	—16	— 4	0.71	65	16.0	3.99	107	79	
8	1-2	..	— 4	....	0.78	97	14.5	4.92	131	96	
K. K.	3	1	+11	+15	0.95	123	18.8	6.91	142	99	+
	4	35	+18	+22	0.63	124	18.1	5.78	142	87	++
9	1-2	..	— 5	....	0.81	73	21.5	5.77	113	86	
F. K.	3	19	+13	+18	0.83	92	21.6	6.70	122	91	
	4	36	+16	+21	0.79	90	21.3	6.68	127	87	+
	5	94	+ 8	+13	0.76	84	22.2	6.19	120	90	
	6	110	+ 5	+10	0.78	82	21.2	5.97	119	90	
10	1-2	..	+ 2	....	0.77	64	23.5	5.72	115	83	
J. K.	3	20	+29	+27	0.81	75	21.3	7.08	124	85	
	4	65	+10	+ 8	0.73	76	20.0	5.69	115	90	
11	1-2	..	—12	....	0.82	...	12.9	4.62			
E. McC.	3	10	+ 1	+13	0.81	...	14.1	5.07			
	4	23	+12	+24	0.81	...	15.7	5.83			
	5	78	—16	— 4	0.94	...	11.0	4.81			
12	1-2	..	+16	....	1.08	79	15.4	9.27	133	100	
J. S.	3	10	+22	+ 6	0.93	76	15.9	8.90	126	86	
	4	34	+43	+27	0.90	100	18.9	9.93	158	95	+
	5	67	+31	+15	1.07	84	16.2	10.27	129	98	
13	1-2	..	+18	....	0.83	65	45.7	10.80	143	108	
F. S.	3	21	+58	+20	0.81	75	58.3	14.56	149	94	
	4	55	+34	+16	0.81	68	63.8	15.22	132	94	
	5	83	+18	± 0	0.82	72	58.7	14.74	120	102	

This increase in the metabolism is expressed partly by a greater oxygen deficit in the expired air, but far more by an increased amount of air breathed as is shown by the greatly augmented minute volumes. This increase in the minute volume is as invariable as is the rise in metabolism. The amount of air breathed per minute was increased as much as two liters in a considerable number of cases.

This response in minute volume is generally, but not invariably, dependent upon increase in both rate and depth of respiration. In a number of cases, however, only one of these factors responded. This is especially true in the subjects with a negative reaction. In those with a positive reaction, regardless of whether rate changed, depth of respiration was consistently augmented with one interesting exception (Case 13, Table 1), who was already breathing at a rate which tended to preclude increase in depth.

TABLE 6.—Correlation of Metabolic and Reaction Data on "Epinephrin Positive" Patients with Hyperthyroidism

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
32	1-2	..	+61	....	0.75	...	19.8	7.66			
R. J.	3	10	+81	+20	0.83	133	21.3	9.21			
	4	26	+78	+17	0.76	134	21.3	8.94			
33	1-2	..	+42	....	0.80	94	18.0	7.22	126	85	
T. M.	3	12	+71	+29	0.86	120	18.2	9.12	147	91	++
	4	41	+71	+29	0.86	122	19.5	9.61	147	95	+
	5	91	+59	+17	0.83	119	17.9	8.70	135	88	+
34	1-2	..	+35	....	0.78	109	19.1	8.46	131	74	
E. S.	3	6	+71	+36	0.96	130	18.6	11.68	154	71	++
	4	31	+59	+24	0.78	137	18.1	9.99	149	62	+

In the positive cases one metabolism period was taken as nearly as possible at the height of the epinephrin reaction, and it was at this point that the greatest metabolic increase was found. Since, however, the periods during which the metabolism was determined were at the height of the reaction and not immediately before and after the apex, one cannot decide definitely whether the caloric elevation shortly precedes or occurs simultaneously with the reaction changes. It can merely be stated that there is a large metabolic increase during the period of maximum change in pulse, blood pressure and symptoms; and that there is a direct relationship between this increase and the reaction changes. It can in no way be stated that the increase is due to the changes.

For a satisfactory comparison with the positive cases, it was necessary in the negative cases, due to the absence of any reaction, to take a metabolism period at a time interval following the injection which synchronized with the maximum point of reaction in the hypersensitive cases. Under these conditions, the negative cases, while never giving a metabolic response equal to that at the apical point of the positive cases, showed a tendency to reach their maximum of change at a period earlier than the time of apical change in the positive cases.

This necessitates reiteration of the fact that the maximum metabolic increase in the "epinephrin sensitive" cases may also occur before the time of apical reaction change.

TABLE 7.—Correlation of Metabolic and Reaction Data on "Epinephrin Negative" Patients with "Irritable Heart"

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min., S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
14	1-2	..	+ 7	....	0.87	58	17.5	7.50	123	75	
N. A.	3	5	+14	+ 7	0.86	65	17.6	7.90	133	66	
	4	32	+21	+14	0.82	64	19.6	8.55	148	62	
15	1-2	..	+16	....	0.85	84	16.0	6.44	142	84	
A. C.	3	5	+23	+ 7	0.90	80	18.1	7.44	146	81	
	4	31	+21	+ 5	0.86	90	19.0	7.40	161	76	
16	1-2	..	+ 9	....	0.78	74	6.5	4.28	136	80	
F. C.	3	5	+14	+ 5	0.82	77	8.5	4.91	136	75	Slight
	4	35	+19	+10	0.77	77	7.3	4.83	136	72	Slight
17	1-2	..	− 9	....	0.77	74	11.0	4.18	97	70	
E. G.	3	18	+ 2	+11	0.82	80	9.9	4.70	102	67	
18	1	..	− 7	....	0.82	72	17.7	5.08	110	78	
L. J.	2	5	+ 2	+ 9	0.81	71	18.9	5.61	115	75	
	3	40	± 0	+ 7	0.76	76	19.1	5.57	118	75	Slight
	4	76	− 5	+ 2	0.76	70	18.1	5.04	113	77	Slight
19	1-2	..	+ 8	....	0.81	69	28.8	6.91	104	72	
J. L.	3	15	+23	+15	0.87	71	36.3	8.70	111	73	
	4	31	+24	+16	0.87	75	38.1	9.03	103	73	
20	1-2	..	− 5	....	0.78	60	10.1	4.31	139	90	
R. L.	3	5	− 3	+ 2	0.81	73	10.7	4.23	149	86	Slight
	4	34	+ 2	+ 7	0.77	72	11.1	4.69	146	79	
21	1-2	..	−10	....	0.79	61	24.8	5.66	107	75	
M. H.	3	22	± 0	+10	0.85	71	22.8	6.42	104	68	
	4	39	−21	−11	0.80	70	23.1	4.83	106	66	
22	1-2	..	+10	....	0.82	72	18.0	6.00	129	86	
O. N.	3	33	+17	+ 7	0.79	80	18.8	6.21	120	71	
23	1-2	..	− 8	....	0.80	52	....	4.82	101	65	
M. T.	3	16	+11	+19	0.87	58	....	5.70	115	59	Slight
	4	31	+ 1	+ 9	0.78	64	....	4.79	111	58	
24	1-2	..	− 3	....	0.81	72	12.8	4.38	123	95	
I. Z.	3	5	+ 5	+ 8	0.84	71	13.8	5.13	126	90	Slight
	4	39	+ 5	+ 8	0.83	72	14.4	5.49	130	90	Slight
25	1-2	..	+12	....	0.85	71	18.3	7.23	138	70	
D. E.	3	5	+16	+ 4	0.87	71	20.0	7.24	143	68	
	4	35	+21	+ 9	0.84	70	20.5	7.83	150	70	Slight

Any interpretations to be based on changes in the respiratory quotient must always be made with due consideration of the mechanical factors that may influence the quotient in periods as short as those in the Tissot method. With these factors in mind, we were inclined to disregard the respiratory quotient in this report as of any value in showing changes in the percent usage of the foodstuffs. But a careful analysis of the tables shows such a total disregard as unjustified. In a large percentage of the cases after injection, the respiratory quotient

shows an increase over the basal value. And this increase very frequently occurs before the maximal changes in respiratory volumes and metabolism. Fuchs and Roth[8] noted this same fact. A changing depth of expiration could, of course, account for this. However, the very facts that this change in the quotient occurred before the time of deepest respiration, that it also often shows in periods long enough after the injection for lung adjustment to have taken place, and finally, that it often persists above basal values for some time, would argue against simple pumping out of carbon dioxid as the cause of the elevation. The elevation must be considered as significant of increased combustion of carbohydrate. Furthermore, the hyperglycemia shown by others after epinephrin injection and found in these cases by us, together with the increased metabolism, give even more significance to the rise in respiratory quotient as indicative of stimulated carbohydrate combustion.

TABLE 8.—Correlation of Metabolic and Reaction Data on "Epinephrin Negative" Patients—All Normal Men

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Min.	Symptoms
26	1-2	..	— 3	....	0.87	56	13.9	5.79	120	79	
F. B.	3	31	+ 7	+10	0.91	58	16.4	6.97	125	74	
27	1-2	..	+ 5	....	0.87	74	16.7	5.43	134	80	
G. F.	3	4	+ 7	+ 2	0.95	75	17.5	6.02	132	82	
	4	34	+13	+ 8	0.91	82	17.9	6.17	138	78	+
28	1-2	..	+ 2	....	0.82	63	9.6	4.98	102	68	
W. J.	3	3	+ 5	+ 3	0.89	64	14.3	5.91	102	70	
	4	39	+12	+10	0.78	63	10.9	5.80	116	69	
	5	96	— 3	— 5	0.85	71	9.6	5.22	112	69	
29	1-2	..	—14	....	0.77	66	12.0	4.67	113	83	
J. K.	3	2	—11	+ 3	0.79	70	12.0	4.98	113	84	
	4	37	— 3	+11	0.76	69	12.1	5.20	116	77	+
	5	84	—17	— 3	0.68	66	11.0	4.06	114	79	
30	1-2	..	+14	....	0.81	77	22.8	7.58	134	82	
R. L.	3	36	+20	+ 6	0.78	75	23.1	7.04	140	69	+
31	1-2	..	+13	....	0.83	71	11.1	6.31	120	80	
J. R.	3	3	+21	+ 8	0.87	66	11.3	7.00	123	80	
	4	34	+18	+ 5	0.75	65	11.5	6.19	118	78	

These various metabolic changes bring up two questions—namely, why is there a rise in metabolism after epinephrin injection, and why is this rise so definitely greater in certain subjects than in others?

In consideration of the first question, as to why there is a metabolic increase after epinephrin injection, one may consider a number of possibilities. The much discussed activity of heart and lungs is perhaps to be taken into account. We have shown, however, in cases

of "irritable heart" that normally there may often be an increase in respiratory activity as great as any seen under the effects of epinephrin without changes in the basal metabolism.[13] In regard to the pulse activity, it is to be noted that the "negative" epinephrin reactions, while showing, to be sure, slight increase in the respiratory activity, showed often no pulse acceleration and yet definite metabolic stimulation. As a further study of the effect of pulse acceleration on the metabolism, we made determinations, which are to be published later, on a number of both "epinephrin positive" and "negative" cases after the injection of 1.2 mg. atropin. In both cases the pulse rate showed increases greater than was general in "positive" epinephrin reactions, and yet there was no metabolic rise. Therefore, respiration and heart activity cannot account for the general rise in metabolism under epinephrin, though it might possibly be responsible in a slight degree for the grade of increase in the positive cases. In fact, the increase in metabolism is more conceivably the cause for increased respiratory and circulatory activity than vice versa.

The excitement attendant on injection might be considered the cause for metabolic increase. In opposition to this there are two facts—first, the rise in metabolism is greater some time after the injection than immediately following it, and secondly, we carried out control determinnations upon positive cases, patients with hyperthyroidism and normal men after the injection of sterile water and found no change in metabolism.

As mentioned above, one of the objective symptoms of the epinephrin reaction is tremor. In the negative cases little gross tremor is visible, but there may be a general increase of muscular tonus, and this might account for a rise in oxygen consumption.

Another possible cause for the rise in metabolism is the hyperglycemia due to the action of epinephrin. This has been considered by practically every experimenter in the field. Carbohydrate plethora results in increased metabolism, which is at the expense of the carbohydrate as shown by the simultaneous elevation of the respiratory quotient. The elevation in the metabolism and the respiratory quotient under epinephrin can thus very plausibly be attributed to the known hyperglycemia resulting from the epinephrin.

All previous experimenters have also discussed the possibility of epinephrin as a direct stimulant to cellular metabolism in general. With regard to this contention there is little evidence one way or the other at the present time. It is, however, generally accepted that

13. Peabody, F. W., Wearn, J. T., and Tompkins, E. H.: The Basal Metabolism in Cases of True "Irritable Heart" of Soldiers, Med. Clin. of North America **2**:507, 1918.

epinephrin has a definitely selective action on the sympathetic autonomic nervous system. It is probable, therefore, that the epinephrin acts indirectly in causing an increase in the metabolism, and it is by acting through the sympathetic system that it produces the changes — the tremor, hyperglycemia, etc.—which are probably the actual causes of the increased heat output.

And it is probably in this selective action of the epinephrin on the sympathetic autonomic nervous system that an explanation is to be sought for the differences of response to a given injection of epinephrin in the individuals with the "irritable heart" syndrome. A difference in the sensitivity of the system to the drug possibly accounts for the differences in response of the individuals studied.

CONCLUSIONS

1. Intramuscular injection of epinephrin causes an increase in total gaseous metabolism in normal men, patients with "irritable heart" and in hyperthyroidism.

2. The increase in metabolism is greater in cases showing a "positive" reaction to the epinephrin than in those showing no characteristic reaction, and it is parallel to the pulse, blood pressure and symptomatic changes.

3. There is an increase in the minute volume of air breathed under the effects of epinephrin, and of either respiratory rate or depth, or both.

4. After intramuscular injection of epinephrin there is very frequently an elevation of respiratory quotient. The maximum of this elevation ordinarily precedes that of the metabolic increase.

5. The increase in metabolism is due to some factor other than the excitement attendant on injection or the stimulation to heart and respiratory muscles resulting from injection.

6. The increase in metabolism may be due to increased muscular tonus, or to hyperglycemia. It may be that these factors are only partial expressions of a general indirect stimulus to the metabolism from the epinephrin by its action on some system capable of direct metabolic activation.

7. As epinephrin is a stimulant to the sympathetic autonomic nervous system, the differences in reaction and metabolic response in the negative and positive cases are probably due to differences in that system.

STUDIES ON EPINEPHRIN. III

EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAMS OF PATIENTS WITH "IRRITABLE HEART"

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INTRODUCTION AND METHODS

This electrocardiographic study was stimulated by the observation of the effect of epinephrin on "irritable heart" cases. In a number of these cases (about 60 per cent.), from twenty to fifty minutes after the injection was made very pronounced changes were induced. There was considerable rise in blood pressure and pulse rate, the patients became dyspneic, complained of precordial pain and dizziness, their hands became cold and tremulous, they became conscious of palpitation, etc.—in a word they seemed to be suffering from the sort of symptoms which had been the original cause for admission to the hospital. In normal trained soldiers this injection produced changes which were essentially negligible.

On account of the effect of epinephrin on the circulation it seemed desirable to find out whether electrocardiographic tracings would show any changes during the occurrence of these symptoms. About eighteen cases of "irritable heart" were studied. The first eight were studied in conjunction with metabolism studies made by Lieut. Joseph T. Wearn, M. C., U. S. A., and Miss Edna H. Tompkins. The tracings, in general, showed a number of different abnormalities which are reported below. A special series of twelve cases was then studied to work out in detail the electrocardiographic changes which might be produced by the drug. Another series of twelve normal men was then studied under identical conditions. The following tabulation contains a classification of the various abnormalities which were found in the electrocardiograms taken at the height of the epinephrin reaction in the first group of eight cases:

TYPES OF CHANGE NOTED AFTER EPINEPHRIN

1. Changes in the P-wave:
   - (a) General lowering of wave in all leads.
   - (b) Sinus arrhythmias which have been seen before the injection have become very pronounced after the injection.
   - (c) Inversion of P-wave and return to normal in the same record.
   - (d) Interpolated P-wave.

2. Changes in Conduction:
   (a) Delayed conduction.
   (b) Partial heart block.
3. Changes in T-Wave:
   (a) General lowering of wave in all leads.
   (b) Diphasic T-wave.
   (c) Inverted T-wave.
4. Effect on Ventricular Muscle:
   (a) Cases showing occasional extrasystoles before injection have shown showers of them after injection.
   (b) Extrasystoles induced in cases which normally have shown none.
5. Changes in Heart Rate:
   (a) Rate at the conclusion has been lower than in the first normal tracing.

These eight cases were not the subject of systematic electrocardiographic study. It was only when the observer noted gross cardiac irregularities that records were made. The changes observed, however, were so striking that they led to a further detailed study of the effect of epinephrin on the electrocardiogram. Twelve men who were hypersensitive to epinephrin were next studied, and in conjunction with these twelve normal men in whom the injection of epinephrin produced no reaction were studied.

TABLE 1.—"Irritable Heart" Cases. Blood Pressure and Pulse Chart

Initials	Normal Systolic Pressure*	Systolic Pressure at Height of Reaction	Time for Rise, Min.	Normal Diastolic Pressure*	Diastolic Pressure at Height of the Reaction	Time for Fall of Systolic Pressure, Min.	Average Pulse Rate before Injection	Average Pulse Rate at Heigth of Reaction†	Pulse Rate at the Conclusion of Reaction
W. S.	108	120	32	56	54	35	71	82	74
J. F.	127	144	36	76	70	15	77	94	86
J. B.	121	138	32	72	60	34	78	86	76
R. W.	104	120	35	69	60	98	62	76	70
J. F.	113	120	18	74	80	10	81	82	76
M. F.	130	138	43	98	100	42	88	100	84
A. M.	88	106	10	49	55	80	72	92	74
F. S.	125	138	33	81	70	30	68	80	72
W. T.	103	113	44	51	60	32	69	86	76
D. C.	119	130	23	73	70	78	73	70	76
W. H.	94	110	40	62	64	30	66	80	72
S. D.	107	126	13	74	96	05	72	98	72
Average	110	125	30	70	70	45	73	86	76

* Obtained by averaging all the readings taken before the injection (average of six readings for each case).
† Nearest reading to the systolic height, sometimes three minutes before the blood pressure height, sometimes three minuts later.

EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAM OF EPINEPHRIN-SENSITIVE INDIVIDUALS

The method used in these cases was as follows: First the patient was put to bed and kept quiet until the blood pressure became constant. When several readings at ten minute intervals showed a constant blood-pressure level, an electrocardiogram was taken. These were begun,

on an average, about forty-five minutes after the patients were put to bed. This electrocardiogram was adopted as a normal for the individual case.

Seven and a half minims of a 1:1,000 solution of epinephrin chlorid (freshly prepared from Parke, Davis & Co.'s adrenalin chlorid tablets) was then injected intramuscularly at the base of the deltoid. Bloodpressure readings were then taken every three minutes until the height of the rise was determined after which they were taken every ten minutes until it again reached normal. A second electrocardiogram was taken at the height of the response to epinephrin, and a third one

Fig. 1.—"Irritable heart" case. Record taken one and three-quarters hours after epinephrin injection. Lead I, P-R time 0.24 second; Lead II, P-R time 0.28 second; Lead III, P-R time 0.28 second. Blocked P-wave.

was taken at the time when the reaction was completed as shown by a return of the systolic pressure to the original level and a fall of the pulse to its level.

From Table 1 it appears that the characteristic reaction after the injection of epinephrin was a rise of the systolic blood pressure (the diastolic pressure remaining unchanged) and an increase in pulse rate. The reaction came on, on an average of thirty minutes after the injection, was manifested by an average increase of 15 mm. in the systolic

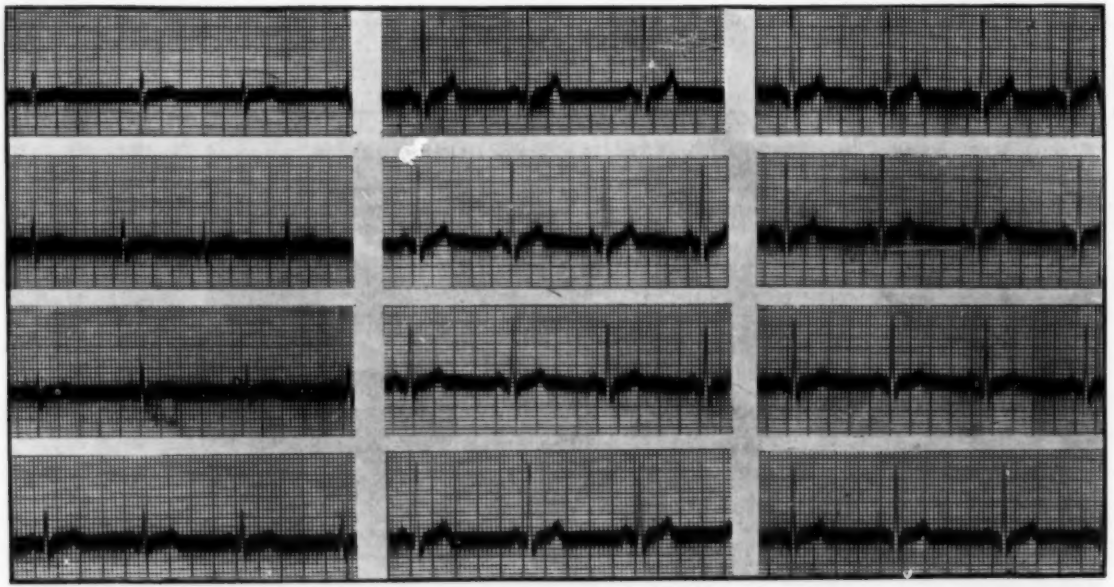

Fig. 2.—Effect of adrenalin on the normal electrocardiogram.

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
1. Before epinephrin injection (after 45 min. rest).....	57	0.16	0.34	1.00	60	0.16	0.36	4.00	65	0.18	0.34	4.00
II. 30 minutes after epinephrin injection.....	65	0.16	0.36	1.00	60	0.16	0.36	2.50	60	0.16	0.36	2.00
III. 1 hr. 15 min. after injection.....	57	0.16	0.36	1.00	62	0.16	0.36	2.00	62	0.16	0.36	1.50
IV. 24 hrs. after I (after 45 min. rest).....	68	0.16	0.34	1.50	60	0.16	0.36	3.00	62	0.16	0.34	2.50

pressure and an increased pulse rate (13 beats) and subsided in forty-five minutes.

After the completion of the blood pressure and pulse observations each patient was asked a series of questions: First, the symptoms which had originally caused him to report to the infirmary and their duration; second, the symptoms which he experienced after the injection, and third, whether he had ever had any similar symptoms before. In trying to interpret the results of this quizzing we had impressed on us con-

TABLE 2.—"Irritable Heart" Cases. Before Epinephrin

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	68	0.12	0.32	2.00	68	0.14	0.32	3.50	73	0.14	0.32	1.50
J. F.	86	0.14	0.30	2.50	91	0.14	0.30	4.00	83	0.14	0.32	1.50
J. B.	91	0.12	0.28	1.00	81	0.14	0.32	2.00	88	0.14†	0.32	1.50
R. W.	52	0.14	0.36	4.50	55*	0.18	0.36	6.00	57*	0.18	0.38	1.50
J. F.	79	0.14	0.30	4.00	70	0.16	0.30	3.50	76	0.16	0.34	1.00§
M. F.	94	0.12†	0.28	3.00	94	0.12	0.32	5.50	94	0.14	0.30	2.50
A. M.	94	0.14	0.30	3.50	80	0.16	0.32	4.00	88	0.16	0.34	1.50—
F. S.	65	0.14	0.34	2.50	70	0.14	0.36	3.00	71	0.14	0.36†	0.00
W. T.	68*	0.12	0.32	3.50	53	0.14	0.34	5.50	71	0.14	0.34	2.50
D. C.	76‡	0.16	0.34	2.00	74‡	0.16	0.34	2.50	74‡	0.18	0.34	1.00
W. H.	72	0.16	0.36	2.00	65	0.18	0.36	6.00	74	0.16	0.36	2.50
S. D.	80	0.12	0.30	2.00	88	0.16	0.32	3.50	80	0.16	0.30	2.00
Aver.	77	0.13	0.31	2.70	74	0.15	0.33	4.08	77	0.15	0.33	1.75

* Marked sinus arrhythmia. ‡ Frequent ventricular extrasystoles. § Diphasic T-wave.

TABLE 3.—"Irritable Heart" Cases. Height of Epinephrin Reaction

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	76	0.12	0.32	1.50	76	0.14	0.34	1.50	76	0.12	0.36	0.50
J. F.	85	0.14	0.34	3.00	79	0.14	0.36	3.50	80	0.14	0.34	1.00
J. B.	74	0.14	0.34	1.00	72*	0.14	0.36	2.00	79	0.14	0.34	1.50
R. W.	70	0.16	0.36	3.00	71*	0.16	0.36	4.00	68	0.16†	0.36	1.50
J. F.	74*‡	0.14	0.34	3.00	74*	0.16	0.32	3.50	66¶	0.16	0.32	1.50
M. F.	96	0.12	0.30	3.00	90	0.14	0.32	4.50	85	0.12	0.32	1.50
A. M.	66*	0.16	0.36	2.00	74*	0.16	0.36	2.50	68	0.16	0.36	0.50
F. S.	76	0.14†	0.34	1.00	74	0.14	0.36	1.50	71¶	0.12†		T-3 absent
W. T.	85	0.14	0.32	2.00	80	0.16	0.32	2.50	85	0.16	0.32	1.00
D. C.	88‡	0.16	0.36	1.00	79‡	0.16	0.36	2.00	77	0.18	0.32	1.00
W. H.	71	0.16	0.36	1.50	68	0.16	0.36	2.50	68¶	0.16	0.36	1.00
S. D.	100	0.12†	0.28	1.00	100	0.16	0.32	2.00	100	0.14	0.32	1.00
Aver.	80	0.14	0.33	1.91	78	0.15	0.34	2.66	77	0.14	0.33	1.09

* Marked sinus arrhythmia. ‡ Frequent ventricular extrasystoles. ¶ Notched R-wave.

stantly the fact that we were dealing with varying degrees of intelligence and introspection in these patients. The following symptoms were noted in the histories of the twelve patients studied: Dizziness (11 cases); dyspnea (9 cases); precordial pain (8 cases); fainting (4 cases); palpitation (2 cases); "weak spells" (2 cases); irregularity of the heart (2 cases). After the injection of epinephrin, tremor was observed in ten cases; increased pulsation of the vessels of the neck in seven cases; flushing or pallor in four cases; increased warmth of

the skin in two cases; restlessness and sweating of the hands in one case each. One patient complained voluntarily of precordial pain. On subsequent questioning it appeared that dizziness was experienced by six patients; precordial pain by five patients; blurred vision by four patients; palpitation by four patients; headache by two patients; irregularity of the heart, pressure in arms and legs, weakness, tremor and excitement, each by one patient.

SYMPTOMS AFTER EPINEPHRIN INJECTION

Separate records were kept of the symptoms which were actually observed after the injection of epinephrin, of those volunteered by the

TABLE 4.—"Irritable Heart" Cases. Conclusion of Epinephrin Reaction

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	69	0.12	0.32	2.00	66	0.14	0.36	3.00	66	0.14	0.36	1.50
J. F.	66	0.16	0.36	2.50	71	0.14	0.36	3.50	66¶	0.14?	0.36	1.00
J. B.	65	0.12	0.36	1.00	66*	0.14?	0.36	3.50	65	0.14?	0.36	2.50
R. W.	66*	0.16	0.36	3.50	70*	0.16	0.36	4.50	70	0.16	0.36	1.50
J. F.	76	0.16?	0.34	3.00	71	0.16	0.34	4.00	79¶	0.16	0.36	2.00
M. P.	83	0.14?	0.32	3.00	80	0.16	0.30	5.50	80	0.14	0.34	2.00
A. M.	68	0.16	0.36	3.50	79	0.16	0.36	3.50	63	0.16	0.32	1.00—
F. S.	62	0.14	0.40	2.50	65	0.14	0.38	2.00	65	0.14?	0.36	0.50—
W. T.	81*	0.16	0.36	2.50	76	0.16	0.34	3.00	71	0.16	0.32	2.00
D. C.	81‡	0.16	0.36	1.00	81*‡	0.18	0.36	2.00	70*‡	0.18	0.36	1.00
W. H.	70*	0.16	0.36	1.50	70*	0.18	0.36	3.00	73	0.18	0.36	1.50
S. D.#												
Aver.	71	0.14	0.35	2.36	72	0.15	0.35	3.40	69	0.15	0.35	1.66

* Marked sinus arrhythmia. ‡ Frequent ventricular extrasystoles. ¶ Notched R-wave.
# Record not obtained.

TABLE 5.—Epinephrin Sensitive "Irritable Heart" Cases

	Before Injection			At Height of Reaction			At the End of Reaction		
	I	II	III	I	II	III	I	II	III
Rate	77	74	77	80	78	77	71	72	69
P-R time (second)	0.13	0.15	0.15	0.14	0.15	0.14	0.14	0.15	0.15
R-T time (second)	0.31	0.33	0.33	0.33	0.34	0.33	0.35	0.35	0.35
T-wave (mm.)	2.70	4.08	1.75	1.91	2.66	1.09	2.36	3.40	1.66

patient, and of those which could be brought out by questioning. Ten of the patients stated that the symptoms which they experienced after the injection of epinephrin were the same in nature as those which they had had many times before and for which they had sought medical aid. Two of the patients could make no association between their symptoms and previous experiences. One of the patients said that the attack was more severe than any which he had had before (this patient had ventricular extrasystoles which were increased in number by the epinephrin). Another of the patients complained of a "jarring

sensation" which he had never had before. (The tracing of this patient after epinephrin showed ventricular extrasystoles.)

It will be of interest to compare the three sets of electrocardiograms in these cases: the normals taken when the patients had been quiet in bed for over thirty minutes, when the blood pressure and pulse rate were constant; those taken at the height of the epinephrin reaction when the systolic pressure and pulse rate were elevated and the patients were experiencing their typical symptoms; and finally the records taken at the conclusion of the reaction.

TABLE 6.—Normal Cases. Blood Pressure and Pulse Chart

Initials	Normal Systolic Pressure*	Systolic Pressure at Height, 30 Min. after Injection†	Normal Diastolic Pressure*	Diastolic Pressure at Height, 30 Min. after Injection†	Pulse Rate before Injection	Pulse Rate at Height of Reaction	Pulse Rate at the Conclusion
F. E.	120	120	70	70	74	80	76
H. B.	110	114	80	80	84	72	72
W. J.	100	98	60	60	70	72	72
L. H.	115	120	65	65	73	80	72
G. B.	119	120	80	80	74	76	76
F. B.	116	114	68	66	70	68	68
W. W.	125	120	70	70	65	64	64
E. C.	116	116	70	70	64	76	72
J. D.	107	118	71	70	75	88	84
T. O'C.	97	98	64	60	60	64	68
A. S.	115	114	70	70	72	72	72
A. O.	108	100	60	60	82	84	76
Average	111	112	69	69	71	74	72

* Obtained by averaging all the readings taken before the injection.
† These readings were made about 30 minutes after the injection of epinephrin.

TABLE 7.—Normals. Before Epinephrin

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	68	0.18	0.36	5.00	68	0.14	0.36	3.50	70	0.14	0.22	1.00§
H. B.	81	0.14	0.32	3.50	76	0.16	0.32	4.00	78	0.18	0.34	1.00
W. J.	67*	0.16	0.36	2.00	66*	0.16	0.36	5.00	66*	0.16?	0.36	3.50
L. H.	68†	0.16	0.32	3.00	74†	0.14	0.34	3.00	79*	0.14	0.34¶	1.00§
G. B.	70*	0.20	0.34	5.00	68	0.20	0.36	5.00	75	0.16?	0.36	1.00
F. B.	64*	0.12	0.36	1.50	61*	0.16	0.34	4.00	70*	0.16	0.34	3.00
W. W.	68*	0.12	0.36	2.50	68*	0.12	0.36	7.00	58	0.14	0.36	4.50
E. C.	56†	0.20	0.40	2.00	61*	0.24	0.40	3.00	61†	0.24	0.40	0.50
J. D.	78†	0.16	0.32	2.00	83†	0.16	0.32	3.50	78*	0.18	0.34	2.00
T. O'C.	60	0.14	0.40	3.00	57	0.16	0.38	4.00	62	0.16	0.38	1.00
A. S.	93	0.16	0.34	3.00	71	0.16	0.34	5.00	77*	0.16	0.34	2.00
A. O.	80	0.16	0.34	1.50	83	0.16	0.32	1.50	82	0.16	0.32	0.50§
Aver.	70	0.15	0.35	2.83	69	0.16	0.35	4.04	71	0.16	0.35	1.75

* Marked sinus arrhythmia.
† Very marked sinus arrhythmia.
§ Diphasic T-wave.
¶ Notched R-wave.

METHODS OF MEASUREMENT OF THE ELECTROCARDIOGRAMS

Rate.—The mean rate for each lead was calculated by determining the maximal and the minimal rates in the lead and averaging the results. In all cases in which there was a variation of 0.12 of a second

or more between beats it was considered that sinus arrhythmia was marked in the lead. A variation of from 0.16 to 0.24 of a second was considered to indicate very marked sinus arrhythmia.

R-T Time.—This was determined by measuring the time interval between the Q-wave and the end of the T-wave. It was possible to measure this to within a half millimeter error.

TABLE 8.—NORMALS. HEIGHT OF EPINEPHRIN REACTION

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	83	0.16	0.34	3.00	93	0.16	0.36	1.50	93	0.16	0.32¶	0.50§
H. B.	75	0.16	0.36	2.50	75	0.16	0.36	3.50	78	0.18	0.32	1.00
W. J.	62	0.16	0.38	1.50	73*	0.16?	0.40	3.50	67†	0.16?	0.36	2.50
L. H.	82†	0.16	0.34	2.00	83*	0.16	0.34	2.00	81*	0.16	0.32¶	0.50§
G. B.	78	0.18	0.36	3.00	78	0.20	0.34	3.00	83	0.18	0.34¶	1.00—
F. B.	66*	0.12	0.36	1.00	70*	0.14	0.36	1.50	68*	0.16	0.36	1.00
W. W.	60	0.12	0.36	1.00	60	0.14	0.40	5.00	60	0.14	0.36	4.00
E. C.	65	0.20	0.42	1.50	70*	0.24	0.40	1.50	71†	0.22	0.40	0.50
J. D.	85*	0.16	0.34	1.50	85	0.16	0.34	3.00	83	0.16	0.34	1.50
T. O'C.	64*	0.14	0.40	2.50	65	0.16	0.38	2.50	65	0.16	0.38	1.50
A. S.	75	0.14	0.36	2.00	75*	0.16	0.36	3.50	71	0.16	0.36	1.50
A. O.	78	0.14	0.36	1.50	77*	0.16	0.34	1.00	78	0.16	0.34?	0.50
Aver.	72	0.15	0.36	1.91	75	0.16	0.36	2.62	74	0.16	0.35	1.36

* Marked sinus arrhythmia. § Diphasic T-wave.
† Very marked sinus arrhythmia. ¶ Notched R-wave.

TABLE 9.—NORMALS. CONCLUSION OF EPINEPHRIN

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	77*	0.16	0.36	3.00	77*	0.16	0.36	2.50	88	0.16	0.32	1.00—
H. B.	71	0.16	0.36	3.00	68	0.16	0.36	3.50	68	0.16?	0.36	1.00
W. J.	58*	0.16	0.36	1.50	65	0.16	0.40	6.00	62	0.16	0.40	4.00
L. H.	69†	0.14	0.36	2.00	67†	0.14	0.36	1.00	71*	0.16	0.34¶	1.00
G. B.	71	0.20	0.36	4.50	78	0.20	0.36	3.50	71*	0.16	0.32¶	1.00—
F. B.	72†	0.14	0.36	1.00	64*	0.16	0.36	2.00	70†	0.16	0.36	1.00
W. W.	62	0.14	0.36	2.00	62	0.14	0.36	5.00	57	0.14	0.36	4.00
E. C.	66*	0.24	0.40	2.00	62	0.24	0.40	3.00	64*	0.24	0.40	1.00
J. D.	74*	0.16	0.34	1.50	78	0.16	0.34	3.00	88	0.16	0.34	2.00
T. O'C.	65†	0.14	0.38	3.00	65	0.16	0.40	3.00	62	0.16	0.38	1.00
A. S.	65	0.16	0.36	3.00	68	0.16	0.36	4.50	73*	0.16	0.36	2.00
A. O.	75	0.16	0.34	1.50	75	0.16	0.36	1.50	75	0.16	0.36?	0.50—
Aver.	68	0.16	0.36	2.33	69	0.16	0.36	3.20	70	0.16	0.35	1.88

* Marked sinus arrhythmia. § Diphasic T-wave.
† Very marked sinus arrhythmia. ¶ Notched R-wave.

All measurements were made under a reading glass, and it is believed that careful measurements by this method involved an experimental error of not more than half a millimeter, which is believed to be the best that can be done. Measuring under magnification certainly reduced the error a great deal. The various tables of measurements were made consecutively, i. e., all the "normals" were measured first, then the records at the "height of the epinephrin reaction," and finally the records at the "conclusion." This was done in order to avoid all possibility of prejudice in measuring the records.

The galvanometer fiber used in these studies was made of glass quartz covered with a gold plate. Lieut. F. W. Keyes, S. C., U. S. Army, maker of the fiber, gives the following data: Length of fiber 13.5 cm.; diameter of fiber, 3.00 microns; resistance, 4,620 ohms; deflection time, 0.02 of a second. The galvanometer was designed by Capt. Horatio B. Williams, Eng. Corps, U. S. Army, for research purposes.

TABLE 10.—Summary of Normal Cases

	Before Injection			30 Minutes after Injection			75 Minutes after Injection		
	I	II	III	I	II	III	I	II	III
Rate	70	69	71	72	75	74	68	69	70
P-R time (second)	0.15	0.16	0.16	0.15	0.16	0.16	0.16	0.16	0.16
R-T time (second)	0.35	0.35	0.35	0.36	0.36	0.35	0.36	0.36	0.35
T-wave (mm.)	2.83	4.04	1.75	1.91	2.62	1.36	2.33	3.20	1.88

In the twelve cases hypersensitive to epinephrin, which were the subject of careful electrocardiographic study, many of the gross irregularities noted incidentally in the first group of eight cases, did not occur. Thus no changes were noted in the conduction time. Inasmuch as control records were obtained before the injection and after the reaction was completed, as well as at the height of the reaction, a basis was obtained for observing any effect on the length of systole and the height of the T-wave. The length of systole, as represented by the R-T time of the electrocardiogram, was not affected by the injection of epinephrin. In lead I the average height of the T-wave before the injection was 2.70 mm. This dropped to 1.91 mm. at the height of the reaction, and rose to 2.36 mm. at the end. In lead II the average height of the T-wave before injection was 4.08 mm., 2.66 mm. at the height of the reaction, and 3.40 at the end of the reaction. In lead III the average height of the T-wave was 1.75 mm. before the injection, falling to 1.09 mm. at the height of the reaction and measuring 1.66 mm. at the end.

There is, then, a slight but perfectly definite decrease in the height of the T-wave at the height of the epinephrin reaction. This is seen, in the averages, in all three leads. Apparently, this change is of relatively short duration, since the records taken at the conclusion of the reaction show the T-wave gradually increasing to the height found before the injection was made. Electrocardiograms were taken of several cases the day after the injection and in all the T-wave was found to have increased to its former height.

It had at first seemed possible that the symptoms complained of by the patients at the height of the epinephrin reaction might be due to changes in the action of the heart. The evidence of the electrocardiogram does not, however, confirm this suggestion. Some of the patients noted symptoms during the reaction while others did not, and the effect on the electrocardiogram was usually very slight and practically the same in all cases.

TABLE 11.—Comparative Table of Height of T-Waves of "Irritable Heart" and Normal Cases

	Lead I				Lead II				Lead III			
	Irritable Heart	Decrease	Normal Cases	Decrease	Irritable Heart	Decrease	Normal Cases	Decrease	Irritable Heart	Decrease	Normal Cases	Decrease
A	2.70	....	2.83	....	4.08	....	4.04	....	1.75	....	1.75	....
B	1.91	0.79	1.91	0.92	2.66	1.42	2.62	1.42	1.09	0.66	1.36	0.39
C	2.36	0.34	2.33	0.50	3.40	0.68	3.20	0.84	1.66	0.09	1.88	+0.13

A. Before injection of epinephrin.
B. At height of epinephrin reaction (30 minutes after the injection, in the case of normals).
C. At conclusion of epinephrin reaction (75 minutes after the injection, in the case of normals).

NORMAL CASES

Following the studies made on cases of "irritable heart," a series of twelve normal men was studied. These men were all overseas men who had been under fire. They came from the surgical service; they were all ambulatory and had been sent to this hospital for convalescence. Their wounds were all healed and none had had any cardiac trouble or had shown the symptoms of "effort syndrome."

EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAM OF NORMAL CASES

The methods used in studying these cases were the same as those used in studying the "irritable heart" cases. The second electrocardiogram, representing the effect produced at the height of the epinephrin reaction, was taken about thirty minutes after the injection. This time interval was found to represent the average time for the height of the reaction in the "irritable heart" cases. The final electrocardiogram was taken forty-five minutes after the second record, which was found to be the average time required for the reaction to pass off completely in the "irritable heart" cases. During this interval between the second and the third electrocardiograms of normal cases blood pressure and pulse observations made at ten minute intervals showed no delayed rise in the normal cases.

From Table 6 it appears that epinephrin has slight effect on either systolic blood pressure or pulse rate in normal men. Similarly, no pronounced subjectve symptoms were produced in this group, in contrast to the results in cases of "irritable heart."

Table 11 shows a comparison of the height of the T-wave in normals and in cases of "irritable heart" before the injection, at the height of the reaction, and at the conclusion of the reaction. No appreciable difference exists between the two types of cases, in fact, in a number of instances, the figures are practically identical. It is thus interesting that in the normal subject there is a complete absence of symptoms which are characteristically produced by the injection of epinephrin in patients with "irritable heart."

CONCLUSIONS

1. The effect of epinephrin has been observed in normal individuals and in a number of patients with the symptoms of "irritable heart." All of the latter were hypersensitive to epinephrin in the sense that they gave a much more pronounced reaction to a small dose of the drug than do normal individuals.

2. In some cases gross abnormalities of the electrocardiographic record were observed. The following were the most important deviations from the normal: Changes in conduction (delayed conduction, partial heart block) and the production of ventricular extrasystoles.

3. Special studies were made of the effect of epinephrin on the conduction time, length of systole and height of the T-wave in twelve epinephrin hypersensitive patients with "irritable heart" and in twelve normal men. No changes were found in the conduction time or the length of systole in either type. In both at the height of the reaction there was a decrease in the height of the T-wave.

4. An attempt has been made to correlate the symptoms complained of by the patients with "irritable heart" at the height of the reaction with abnormalities of the electrocardiogram, but no definite association could be made.

It is a great pleasure for me to express my indebtedness to the medical and the surgical staffs of General Hospital No. 9 for interest and cooperation in these investigations. The chiefs of the cardiovascular division, Major Francis W. Peabody and Capt. Bertnard Smith, M. C., U. S. Army, have carefully supervised the work of this laboratory. I am particularly indebted to Lieut. Joseph T. Wearn, M. C., U. S. Army, and Miss Edna H. Tompkins, whose epinephrin studies on "irritable heart" cases stimulated me to undertake these investigations. My laboratory assistants, Lieut. Frederick W. Keyes, S. C., and Serg. Thomas H. Ford, Medical Department, U. S. Army, have given invaluable assistance in the technical work involved in these studies.

AN EXPERIMENTAL ENDOTHELIAL LEUKOCYTOSIS IN GUINEA-PIGS *

FIFTH REPORT OF STUDIES ON THE MONONUCLEAR LEUKOCYTES OF THE BLOOD

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In laboratory animals there may be produced a neutrophilic leukocytosis by infectious agents such as the pyogenic cocci, or by chemical substances such as croton oil. A less striking increase of the eosinophils has been produced by extracts of certain parasitic worms. Aside from the diagnostic significance of variations in the number of leukocytes in human blood, there are indications that the reaction of cells present there is a factor in the resistance to the infection. The development of a method[1] for the identification of endothelial leukocytes made it possible not only to determine the percentage of these cells present normally in the blood of experimental animals, but also to test the effect on the endothelial leukocyte count of bacterial and animal proteins and of chemical compounds. The guinea-pig was chosen for the experiments largely on account of its freedom from natural infections of a chronic nature.

Blood is best obtained from the guinea-pig by snipping with scissors to the distance of 2 or 3 mm. the margin of the shaved and perfectly dry ear, and expressing small drops of blood by compressing and making slight lateral pressure. The covers are touched to the top of the small drops. No less than two dozen smears are made, and four of these are stained by the granular leukocyte stain[1] for the percentage count of leukocytes present. The blood pipet for the enumeration of the white cells is filled at the same time, in order that the total number of the various leukocytes may be determined from the differential counts. The percentage of endothelial leukocytes in normal guinea-pig blood is subject to considerable variation just as it is in human blood. In fifteen animals (Nos. 10, 12, 33, 35, 67, 68, 69, 70, 71, 76, 79, 80, 82, 83 and 86) this varied between 0.5 and 3.1 per cent., with an average of 1.58 per cent.

Synthetic dyes were made the subject of investigation on account of the known property of certain ones to enter the cytoplasm of endothelial cells and leukocytes when introduced as in intravitam

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* From the Department of Pathology, Marquette Medical School.

1. McJunkin, F. A., and Charlton, Alice G.: Arch. Int. Med. **22**:157 (Aug.) 1918.

RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
10	May 9	840	.....	.....	350 cells counted: percentages: L, 64.7; N, 25.6; E, 6.8; B, 0.5; End, 2.4
	May 14	...	1 c.c. heavy suspension B. subtilis intraperitoneally (i. p.)		
	May 15	...	Same as May 14		
	May 17	...	.....	.....	1,430 cells counted: percentages: L, 39.6; N, 50.5; E, 8.4; B, 0.5; End, 1.0
	May 21 (killed)	...	.....	.....	792 cells counted; percentages: L, 48; N, 46.6; E, 2.5; B, 0.6; End, 2.3
12	Nov. 1	385	.....	16,000	595 cells counted; percentages: L, 55.5; N, 42.7; E, 0.3; B, 0; End, 1.5
	Nov. 4	...	.....	14,500	No differential count
	Nov. 5	...	½ slant, B. typhosus i. p.		
	Nov. 7	...	Same as Nov. 5		
	Nov. 8	...	.....	12,500	1,346 cells counted; percentages: L, 47.6; N, 49.5; E, 0.5; B, 0; End, 2.4
	Nov. 12	...	1 slant		
	Nov. 13 (killed)	...	.....	23,000	1,756 cells counted; percentages: L, 22.5; N, 73.2; E, 0.5; B, 0.5; End, 2.3
13	Dec. 4	417	Suspension entire lungs of normal guinea-pig (ground in mortar) i. p.		
	Dec. 9	...	Same as Dec. 4		
	Dec. 11	...	Same as Dec. 4		
	Dec. 16 (killed)	...	.....	19,000	582 cells counted: percentages: L, 36; N, 58.6; E, 2.7; B, 1.0; End, 1.7
17	Jan. 9	650	5 c.c. heavy suspension beef lung (ground in mortar) i. p.		
	Jan. 17 (killed)	675	.....	20,000	968 cells counted: percentages: L, 56.5; N, 25; E, 14.1; B, 1.4; End, 3.0
19	Jan. 9	600	5 c.c. same suspension as No. 17		
	Jan. 13	...	Same as Jan. 9		
	Jan. 17	...	Same as Jan. 9		
	Jan. 22 (killed)	...	.....	.....	860 cells counted; percentages: L, 53.5; N, 27; E, 13; B, 5; End, 1.5
33	Feb. 20	640	.....	11,000	440 cells counted; percentages: L, 39.8; N, 38.7; E, 18.2; B, 1.1; End, 2.2
	Feb. 27	...	10 c.c. of 2 per cent. (approximate) suspension sudan III in 1 per cent. gelatin; i. p.		
	Feb. 28	...	20 c.c.		
	March 3	...	10 c.c.		
	March 4 (dead)	...	10 c.c.	17,000	635 cells counted; percentages: L, 33; N, 62; E, 0.9; B, 0; End, 4.1

* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(*Continued*)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
35	March 5	520	28 mg. arsphenamin; i. p.	12,200	1,318 cells counted; percentages: L, 26.9; N, 68.8; E, 0.2; B, 0.9; End, 3.1
	March 10	...	40 mg. arsphenamin; i. p.		
	March 13 (killed)	...	.....	7,500	792 cells counted; percentages: L, 50.2; N, 34.8; E, 9.5; B, 2.5; End, 3
43	March 12	190	1 c.c. suspension tubercle bacilli (about 8,000 bacilli) of the human type i. p.		
	March 19	215			
	March 26	230			
	March 29	200	.....	35,200 (includes nucleated red cells)	941 cells counted; percentages: L, 17.9; N, 75.2; E, 0.2; R, 0; End, 6.7; numerous nucleated red cells
	April 2	185	.....	.....	Percentages: L, 35; N, 53.5; E, 0.6; B, 1.6; End, 9.3; numerous nucleated red cells
	April 9 (dead)				
44	March 12	385	1 c.c. suspension tubercle bacilli (see No. 43)		
	March 26	245	.....	22,400	1,310 cells counted; percentages: L, 17.7; N, 70.6; E, 0.6; B, 0; End, 11.1; numerous nucleated red cells
	March 30 (dead)				
60	April 4	215	1 c.c. suspension tubercle bacilli human type (about 1 bacillus per oil immersion field i. p.		
	May 26 (killed)	...	.....	7,000	818 cells counted; percentages: L, 40.8; N, 47.6; E, 0.3; B, 1.8; End, 9.5; 94 erythroblasts
62	April 4	385	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 27	190	.....	.....	836 cells counted; percentages: L, 63.9; N, 18.9; E, 0.3; B, 0.6; End, 16.3
	May 28 (dead)				
64	April 4	262	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 16	...	.....	21,900	1,600 cells counted; percentages: L, 22.4; N, 68.3; E, 0.2; B, 0.1; End, 9
	May 26 (killed)	285	.....	36,000	1,610 cells counted; percentages: L, 30.3; N, 60.5; E, 0.2; B, 0.3; End, 8.7; 50 erythroblasts
65	April 4	202	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 20	225	.....	15,500	1,410 cells counted; percentages: L, 42.6; N, 47.2; E, 0.5; B, 0.3; End, 9.4
	May 30 (killed)				

* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(*Continued*)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
67	April 22	635	.....	15,500	942 cells counted; percentages: L, 59.4; N, 31.4; E, 7.4; B, 0.5; End, 1.3
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 2	640	5 c.c.	21,000	1,034 cells counted; percentages: L, 32; N, 59; E, 4.8; B, 0.5; End, 3.7
	May 9	...	5 c.c.	20,200	1,248 cells counted; percentages: L, 34.3; N, 57.5; E, 4.8; B, 0.2; End, 3.2
	May 14 (dead)				
68	April 22	490	.....	13,800	1,120 cells counted; percentages: L, 53.8; N, 40.4; E, 4.3; B, 0.3; End, 1.2
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 2	465	.....	16,100	970 cells counted; percentages: L, 38.1; N, 54.5; E, 0.6; B, 0.4; End, 6.4
	May 9	485	.....	15,800	1,186 cells counted; percentages: L, 21.5; N, 70; E, 3.6; B, 0; End, 4.9; many nucleated red cells
	May 13 (dead)				
69	April 22	375	.....	12,200	975 cells counted; percentages: L, 58.8; N, 33.8; E, 5.6; B, 0.4; End, 1.4
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 1	...	.....	14,200	1,140 cells counted; percentages: L, 33.6; N, 59.3; E, 3; B, 0; End, 4.1
	May 2	380			
	May 8	390	.....	12,800	610 cells counted; percentages: L, 39.8; N, 51.6; E, 4.2; B, 0; End, 4.4; few nucleated red cells
	May 9	...	4 c.c.		
	May 14 (killed)	398	.....	10,900	500 cells counted; percentages: L, 28; N, 62; E, 5.4; B, 0; End, 4.6; many nucleated red cells
70	April 22	437			
	April 23	...	.....	17,000	1,210 cells counted; percentages: L, 46.2; N, 47.8; E, 3.3; B, 0.6; End, 2.1
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, subcutaneously		
	April 30	435	.....	19,500	1,096 cells counted; percentages: L, 31.9; N, 60; E, 3.8; B, 0.8; End, 3.5
	May 2	440	5 c.c.		
	May 7	405	.....	18,800	1,046 cells counted; percentages: L, 28.5; N, 62.7; E, 4.8; B, 0.2; End, 3.8; a few nucleated red cells
	May 9	...	4 c.c.		
	May 14 (killed)	395	.....	24,400	1,166 cells counted; percentages: L, 28.3; N, 66.1; E, 2.4; B, 0; End, 3.2; a few nucleated red cells

* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(*Continued*)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
71	April 22	515	.....	17,000	1,048 cells counted; percentages: L, 37; N, 45.8; E, 13.6; B, 0.8; End, 2.8
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, subcutaneously		
	April 29	480	.....	14,200	1,138 cells counted; percentages: L, 13.5; N, 81.4; E, 0.3; B, 0; End, 4.8
	May 2	475	5 c.c.		
	May 6	...	.....	18,600	1,150 cells counted; percentages: L, 30.4; N, 60.5; E, 4; B, 0.3; End, 4.8
	May 9	...	4 c.c.		
	May 13 (killed)	...	.....	18,400	1,272 cells counted; percentages: L, 33.1; N, 60.8; E, 2.9; B, 0; End, 3.2; 2 nucleated red cells
76	May 16	305	10 c.c. of colloidal solution of sudan III (about 0.5 per cent.) i. p.	8,200	890 cells counted; percentages: L, 52.2; N, 44.2; E, 1.6; B, 0.3; End, 1.7
	May 17	...	10 c.c.		
	May 19	...	10 c.c.		
	May 21 (killed)	285	.....	12,900	1,060 cells counted; percentages: L, 42.5; N, 52.5; E, 2.2; B, 0.3; End, 2.5
79	May 23	405	1 c.c. of 2 per cent. Bismarck brown, i. p.	8,400	415 cells counted; percentages: L, 61.8; N, 37.7; E, 0; B, 0; End, 0.5
	May 26	...	2 c.c.		
	May 27	...	4 c.c.		
	May 28 (killed)	...	.....	17,800	1,225 cells counted; percentages: L, 20.2; N, 78; E, 0.3; B, 0.2; End, 1.3
80	May 26	395	1 c.c. of 2 per cent. eosin, i. p.	8,000	776 cells counted; percentages: L, 61.4; N, 37; E, 0.5; B, 0.5; End, 0.6
	May 27	...	2 c.c.		
	May 28 (killed)	...	.....	7,000	766 cells counted; percentages: L, 63.9; N, 33; E, 0; B, 0.7; End, 2.4
82	June 2	395	0.5 c.c. of 0.25 per cent. crystal violet, i. p.	6,300	608 cells counted; percentages: L, 74; N, 17; E, 7.5; B, 0.5; End, 1
	June 7	415	1 c.c.		
	June 9 (killed)	420	.....	8,300	784 cells counted; percentages: L, 57.5; N, 34.7; E, 5.3; B, 1.2; End, 1.3
83	June 2	355	0.5 c.c. of 0.25 per cent. methylene blue, i. p.	.....	395 cells counted; percentages: L, 53.5; N, 38.5; E, 6.1; B, 0.7; End, 1.2
	June 9 (killed)	380	1 c.c.	7,500	631 cells counted; percentages: L, 53.2; N, 31.7; E, 12; B, 1; End, 2.1
86	June 3	360	0.5 c.c. of 0.1 per cent. night blue, i. p.	7,000	820 cells counted; percentages: L, 59.7; N, 39.2; E, 0.3; End, 0.8
	June 5 (killed)++	...	.....	6,000	313 cells counted; percentages: L, 26.8; N, 72.3; E, 0; B, 0.3; End, 0.6

* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

staining. Grübler's dyes were used in all instances. No increases in endothelial leukocytes were produced by Bismarck brown, eosin (yellowish, water soluble), crystal violet, methylene blue or night blue (Nos. 79, 80, 82, 83 and 86). Sudan III, in large doses, produces quite regularly an increase above the maximum of 3.1 per cent. (No. 35) met with in normal guinea-pigs, and this dye was administered in varying amounts and by different methods in an attempt to produce a marked endothelial leukocytosis extending over a considerable time without killing the animal. This was not successful. The highest count is seen in No. 68, one week after an intraperitoneal injection of the dye in solution in olive oil. The average of fourteen counts taken from Nos. 33, 67, 68, 69, 70, 71 and 76 is 4.1 per cent. In normal guinea-pigs usually more lymphocytes are present than neutrophils, but a few days after a large injection of sudan III the neutrophils are in excess. If the number of eosinophils is great in the untreated animal these are decreased by the action of the dye. A moderate anemia develops and nucleated red cells appear in the blood.

In guinea-pig blood, after staining with a polychrome blood stain, it is even more difficult to identify endothelial leukocytes than it is in human blood since a greater percentage of these cells approaches the lymphocytes in size and shape. With the alphanaphthol stain[1] the endothelial leukocytes have very distinct blue granules often clumped in the indented portion of the nucleus, and in the parts of smears properly spread they are readily identified. The neutrophils have blue granules less distinct than those of human blood and the cytoplasm is practically unstained. The eosinophilic granules appear as large refractive ringlike spherules with a bluish periphery. The large basophilic granules are a deep red or purple. So far as this stain is concerned, there is no basis for offering a classification for the leukocytes different from the one adopted for human blood. The reasons for regarding the mononuclear cell with blue cytoplasmic granules as of endothelial origin have been given fully in previous reports.

The liver, kidneys, adrenals, spleen, omentum, lungs and heart were fixed in Zenker's fluid and stained with eosin-methylene blue. The histologic changes are confined to the abdominal organs of the animals injected intraperitoneally. In the animals receiving aqueous suspensions of the dye, adhesions in the peritoneal cavity, especially about the liver, are marked and microscopically fibroblastic proliferation has taken place in the omentum; here endothelial leukocytes containing particles of the dye have accumulated. The fibrous capsule of the liver is thickened, and directly beneath it the liver cells about the periportal tissue have become necrotic. In No. 70 the necrotic

liver cells are being ingested by endothelial leukocytes. A few mitoses are present in the zona glomerulosa of the suprarenal cortex and scattered necrotic cells are found in the inner portion of the cortex.

The typhoid bacillus which produces an endothelial reaction regularly in human tissue, as shown by Mallory,[2] does not cause an endothelial leukocytosis in guinea-pigs (No. 12). Negative results followed injections of bacillus subtilis. A number of animals were given suspensions of organs made by grinding them up aseptically with sand in a mortar; others received autolysates of guinea-pig lungs, beef lungs and beef spleen. No marked or constant increases were observed (Nos. 13, 17, 19). Asphenamin, ox-bile and solutions of ether proved negative.

Although a moderate endothelial leukocytosis may be produced by intraperitoneal injections of sudan III in amounts that lead to the death of the animal in a few weeks, in no case was an increase to 10 per cent. noted. In the later stages of the tuberculosis in guinea-pigs induced in the usual way, the percentage found in the sudan III experiments is quite regularly exceeded, and the endothelial leukocytosis persists until the animal dies. In view of the small percentage of these cells present in normal guinea-pigs (1.5), the blood picture in tubercular animals, such as No. 62 with the leukocytes reaching 16.3 per cent., is a striking one. The increase may appear within two weeks from the time of inoculation (No. 44). In eight counts on six tubercular animals (Nos. 43, 44, 60, 62, 64 and 65) an average of 10 per cent. of endothelial leukocytes is present. At necropsy the tissues in the six animals present the usual picture with miliary and conglomerate tubercles in the liver and lungs, and caseous masses measuring one centimeter in the greatly enlarged spleen.

CONCLUSIONS

Although there are few endothelial leukocytes normally present in the peripheral blood as compared with the neutrophils or lymphocytes, the percentage may be increased regularly by experimental procedures. It appears after an examination of the usual textbooks and a cursory examination of the literature that a characteristic increase in number in human blood of this variety of leukocyte has not been noted in generalized miliary or other forms of tuberculosis. Such a leukocytosis is present in the later stages of the usual experimental tuberculosis of guinea-pigs.

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2. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.

NECROPSY STUDIES AT A HOSPITAL CENTER*

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INTRODUCTION

The study in this paper covers a vast amount of material examined in a relatively short period of time. It is therefore more extensive than intensive. It is not possible to give an exhaustive discussion of all the lesions encountered—for that would involve little short of an unabridged treatise on pathology—but rather to give a brief and hurried résumé of all of the important pathologic conditions that came under observation. In the period under discussion, more than 30,000 patients passed through the center. At one time more than 20,000 patients and personnel were quartered here. The heavy pressure of work from all sides, together with the absence of proper library facilities, makes it impossible to give much more than a cursory sketch of the grosser details of the postmortem findings.

During the period included between July 23, 1918—when the first convoy of patients arrived at this center—and Jan. 1, 1919, there are recorded a total of 429 deaths. Of this number, about fifteen bodies were not necropsied for reasons other than the lack of time; these dead included nurses, officers from the personnel, allied soldiers, several bodies brought in crushed in railroad accidents, and one case of drowning among the enlisted personnel. The number of necropsies performed during this period was 356, or about 86 per cent. of the total possible number. This percentage is not inconsiderable when one observes the constant and progressive rise in the curve of the number of patients in the hospital during October and the early part of November. The shortage of personnel became very acute and presented itself in the most accentuated form in the laboratory services.

The highest death rate occurred during October, when 245, or considerably more than one half of the total number of deaths occurred. During this month the deaths averaged eight per day, with three deaths as the minimum and fourteen deaths as the maximum. Of these, the majority were due to respiratory diseases. Indeed, the total number of nonwounded men among the 356 cases that came to necropsy was 214, or in excess of 60 per cent.

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The important findings will be discussed in the order of their frequency. (See appended statistical résumé.)

EMPYEMA AND PLEURISY

The most frequent necropsy finding in the entire series was empyema and pleurisy. This occurred in 63.2 per cent. of the series. The degree of pleurisy varied from a few cubic centimeters of serofibrinous exudate to several liters of thick pus. In most of the cases there were fibrinous deposits, occasionally large, shaggy, fibrinopurulent masses. The distinction between empyema and plain pleurisy was at times made only arbitrarily, depending on the quantity and character of the exudate. Real thick creamy pus was of rare occurrence, being present in only about twenty of the cases. The remaining thirty cases classified as empyema were characterized more by a thin, only slightly turbid, serous exudate, containing large fibrinopurulent masses. The abundance of this plastic, shaggy exudate was very striking. It was not at all unusual to find a yellowish-fibrinous deposit from 3 to 4 c.c. in thickness, covering the lower lobes of the lungs. Rarely was the exudate blood tinged. A number of the true empyemas were associated with gunshot wounds of the chest.

Of the "nontraumatic" empyemas, only about 50 per cent. of the cases were diagnosed clinically. In a few cases in which thoracostomy was performed, the drainage tubes were found inserted 2 to 4 inches into the chest cavity, so that from 500 to 1,000 c.c. of pus were still undrained.

Subacute or chronic pleurisy was encountered fifty times, or in 14 per cent. of the cases. A combination of both chronic and acute pleurisy existed in thirty cases, or 8.5 per cent.

The terms "chronic" and "acute" are often misnomers. We term lesions with fibrous adhesions as chronic. Yet these may be of only short duration. A case came to necropsy which demonstrated how quickly these adhesions may arise. A man was wounded by a piece of shrapnel in the chest and was sent to the hospital with a diagnosis of a foreign body in the lung as revealed by the roentgen ray. In the hospital the roentgen ray confirmed the diagnosis until about one day before death, which was twenty-two days after the injury. A roentgenogram taken at this time in a changed position of the patient showed the bullet movable in the pleural cavity. At necropsy there was found a localized empyema in the pus of which was present a small piece of shrapnel. The adhesions walling off this empyema were exceedingly strong and along the entire margin of the "abscess" cavity there were dense, hyalinized, grayish white, connective tissue adhesions, 3 mm. in thickness, which abruptly thinned out over the uninvolved portions of the lung

and pleura. The involved portion of the pleural cavity occupied about two thirds of the space on that side; the rest was entirely normal. The other pleural cavity was also free from lesions. Here, then, was a lesion with dense fibrous connective tissue formation, 3 mm. in thickness, which formed during the short period of twenty-three days.

PNEUMONIA

The next most frequent finding was pneumonia. This condition was present in 218, or 61.2 per cent. of the cases. The intensity of the involvement varied from almost miliary areas of consolidation around the bronchioles, to complete hepatization of entire lobes on one or both sides. Bronchopneumonias were most common, constituting more than three fourths of the cases. These at times were so massive and confluent that they resembled true lobar pneumonias. Some of the cases diagnosed at necropsy as lobar pneumonia, which later proved to be streptococcic infections culturally, were probably of this type.

Cultures and smears from the lungs were taken frequently. The cultures were made by searing the cut surface thoroughly and then, with a glass pipet having a rather large opening, a small quantity of macerated pulp, mixed with expressed fluid, was drawn up and inoculated into appropriate media. The maceration was accomplished by working the end of the pipet up and down into the parenchyma through the sterilized surface.

The frank characteristic lobar pneumonias in the gray hepatization or early resolution stage, as found ordinarily, were very uncommon. Not more than twenty such cases were encountered. The other cases classified under lobar pneumonia were atypical. An entire lobe or even an entire lung was often involved, but this involvement was irregular. The organ, though solid and heavy, was not large, and the cut surfaces were very mottled showing grayish, brownish or dark red areas of hemorrhage and edema with small portions that would still float in water. Areas of necrosis with abscess formation were quite frequent.

One type of pneumonia was encountered that was different from all ordinary pneumonias. In this type the involvement was either of an entire lobe or only of portions of one or several lobes. The involved areas were firm, heavy and had a rubber resiliency. The cut surfaces were dark red or dark brown in color, often showing a mottling with miliary or submiliary yellowish areas. Sometimes there was a fine grayish lace work visible through the reddish parenchyma that suggested thickened alveolar walls. These areas seemed to be most prominent along the bronchial branches. Culturally this type of pneumonia gave invariably a streptococcus, either hemolytic or nonhemolytic.

Microscopically, in the earlier stages, the alveolar walls show a thickening and an infiltration with lymphoid and plasma cells. The alveoli contain serum, red blood cells, a few polymorphonuclear leukocytes and many desquamated epithelial cells. The walls are edematous and the capillaries are dilated. Some show an intense infiltration with polymorphonuclears. In the later stages, the alveolar walls are seen invading the fibrinous plugs in the alveoli. The alveolar walls themselves appear like dense cellular bands of connective tissue, infiltrated with lymphocytes. Some areas show an almost complete fibrosis with practically all of the alveolar structure absent. Here and there may be seen alveoli lined with high cuboidal or even columnar epithelium suggesting attempts at regeneration. The last stage of this pneumonia is identical with the typical chronic, organizing or indurative pneumonias of the textbooks.

The histories in these cases were not at all characteristic, and did not even suggest the type of lesion present. Some cases had a rather acute onset with a history of not much more than a week's duration. Others presented histories extending over two, three or sometimes four weeks.

The frequent gradations from one type of pneumonia to another and the occasional mixture of all the types in a single lung, made it very difficult at times to classify properly the lesions encountered. Histologic study has occasionally demonstrated the existence of interstitial pneumonia where no such diagnosis was made at necropsy grossly; and conversely some cases diagnosed as interstitial pneumonia proved to be only a massive bronchopneumonia with extensive edema and hemorrhage accompanied by very little purulent exudate.

HEART'S BLOOD CULTURES

Blood cultures were taken routinely at all necropsies. The anterior surface of the right ventricle was sterilized with a pronged searing iron and about 5 c.c. of blood removed with a sterile glass pipet. This was inoculated into two or three tubes of dextrose broth. Sometimes a portion of this mixture was plated out in the laboratory. Pneumococci were tested for bile solubility.

The number of positive cultures was high, about 50 per cent. This is considerably higher than in civil life experience. Of this number more than one half showed *S. hemolyticus*. Not a single case of a true *S. viridans* was obtained. The one pure culture of this organism identified came from a blood culture taken a few days before death in a case of septicemia.

B. welchii was recovered through blood culture from several cases in which no gaseous gangrene was present, and from two patients who were not even wounded. The *B. pyocyaneus* was recovered twice in pure culture and three times mixed with other organisms.

GUNSHOT WOUNDS

About 40 per cent. of the cases in this group came to necropsy. This included minor as well as major injuries. In a number of these cases, the wounds had nothing to do with the actual cause of death. The extremities suffered the largest number of injuries. Fractures of the femur and the ilium contributed to death most frequently outside of the direct injuries to the peritoneal cavities which resulted in general peritonitis. Under injuries to the chest were included injuries to the dorsal spine as well as to the thoracic cavity. Every case of spinal cord injury resulted in extensive gangrenous and ulcerative cystitis.

Striking features in the cases of head injuries were the finding of massive destruction of brain tissue in cases up to six weeks after the inception of the injury. More than once, the question that arose in the mind of the pathologist was not why did the patient die or what caused his death, but why did he or how could he live so long?

In many of the gunshot injuries the infection was very great, causing dissecting abscesses to extend up and down the tissues from the point of injury. Sometimes several square feet of skin and muscle tissue were undermined by the spreading infection. In many cases, at the time of necropsy, it appeared that the surgical treatment was altogether too conservative. Often the debridement was not extensive enough, while in other cases a limb was saved at the expense of a life.

OTITIS MEDIA AND SINUSITIS

Very early in the postmortem examinations the presence of pus in the sinuses of the skull was a striking feature. It was most constantly present in cases in which pneumonia was the prominent lesion. When only one sinus was involved, it was usually the sphenoid. One fourth of all the cases showed purulent sphenoidal sinusitis and frequently the pus "welled" up, as soon as the sinus was opened. Otitis media was relatively infrequent and when present contained exudate in a much lesser degree.

Smears and cultures from the pus frequently showed no organisms. When organisms were present they usually corresponded to those found in the cultures from the heart's blood or from the lung. Streptococci and pneumococci were therefore the most common bacteria. The *B. influenza* of Pfeiffer was exceedingly rare, being found in only one case of sphenoidal sinusitis.

The question of etiology is an interesting one. Were the bronchopneumonias, so frequently encountered, secondary to the sinusites, or were the sinusites secondary to the pneumonias? The possibility of a "reversible" reaction has to be admitted. Infected material from the

sinuses might drain down the pharynx and through the larynx gain entrance to the terminal bronchioles where it might set up a purulent bronchitis and a subsequent pneumonia. But the reverse may also occur. A patient in bed with bronchopneumonia cannot help getting the nasopharynx bathed in sputum from whence infection may spread to the sphenoidal and ethmoidal sinuses. Our necropsy material did not aid in clarifying this relationship, since priority in either lesion could not be established. On a few occasions it was thought that the sinusites appeared to be the older lesions.

INFLUENZA

This is not a finding at necropsy; but under this heading are discussed the lesions found at necropsy in eighty-seven cases in which the diagnosis of influenza was present on the field medical card as the cause of the patient's admission to hospitalization. Probably some of these cases were diagnosed wrongly; perhaps some patients died as a result of complications of influenza in which the proper initial diagnosis was not entered.

Of the eighty-seven cases so diagnosed, 86.2 per cent. showed complicating pneumonias. These pneumonias were not greatly dissimilar to other pneumonias except in a few details. First, the percentages of lobar and interstitial types are higher in this group than in the total pneumonias. This may be accounted for by the fact that in these cases the pneumonias played a more important rôle in the causation of death than in the others, since in the total pneumonias many of them were only terminal conditions, secondary to severe wounds, typhoid fever, etc. The percentage of identified pneumococcus pneumonias is also higher.

Abscesses were more frequent. Dilatations of the bronchioles and bronchi were fairly common. Some of the sacculations measured several centimeters in diameter. Some structures that appeared like abscesses were proved on closer observation to be bronchiectases of the saccular type.

Parallel with the high percentage of pneumonias ran the high percentage of sinus involvement. Fifty out of the eighty-seven cases showed this condition.

Meningitis was found in 8 per cent. of the cases admitted as influenza. One of these was a tuberculous case. This may have been a mistaken initial diagnosis, since the early symptoms of the tuberculous meningitis might have simulated influenza. The two cases of pneumococcic meningitis were secondary to pneumonia and empyema, which in turn were probably secondary to influenza. With the four cases of meningococcic meningitis it is difficult to decide whether the influenza

actually antedated the meningococcic infection or whether there was a mistaken initial diagnosis. It has been stated that influenza may increase the susceptibility to meningeal infection, especially meningococcic.

One of the negative findings is worth mentioning—the almost complete absence of recently activated tuberculous lesions by preexisting influenza, a complication frequently mentioned in the textbooks. Reference to the attached statistical résumé will show that the percentage of occurrence of this lesion in the cases of influenza was less than half of that found in the total number of necropsies.

The other associated lesions, such as Zenker's degeneration, septicemia, pericarditis, etc., need no special discussion here. Their frefrequency can be found by referring to the statistical summary accompanying this paper.

A few bacteriologic reflections may be relevant at this point. A careful study of the material, both from the pathologic appearances and from the bacteriologic findings, suggests that the influenza bacillus of Pfeiffer did not play an important rôle in the cases of influenza treated at this center. Out of a total number of 356 necropsies, only three cases revealed a bacillus in cultures or in smears which morphologically and culturally resembled the *B. influenzae*. This was found in one case in smears and cultures of the lung; in another, in smears and cultures from the sphenoidal sinus, and in a third, in cultures from the blood. In these three cases the organisms were present not in pure culture but mixed with pneumococci. Although in a large majority of the cultures made at necropsy, the conditions were favorable for the growth of the influenza bacillus, nevertheless this organism revealed itself very rarely. Neither was it found in direct smears from the pus in the sinuses nor from the lungs. It might be argued that the cases which came to this center were somewhat late in the stage of the disease, and that this fact might explain the absence of the true causative agent and the presence of the secondary invaders. But a casual study of the literature on this subject tends to show that similar findings are not uncommon in many of the laboratories throughout the world. Careful bacteriological studies in some of the camps of the United States have almost convinced the investigators that the *B. influenzae* plays a very unimportant rôle, if any, in the etiology of influenza.

Considering the method of spread, the kind of complications and the character of the lesions found at necropsy, influenza may be considered as a highly contagious, but self-limited disease of unknown etiology, which bears a remarkable resemblance to measles. Indeed, it is convenient to look on influenza as nonexanthematous measles. There are several reasons for such a concept; the extreme contagious-

ness of both diseases associated with coryza, pharyngitis and lacrimation; the inability to demonstrate definitely the causative agent; the relative absence of leukocytosis, which is especially striking as the onset of the complicating pneumonias; the frequency of the pneumonic complications which are nearly always the cause of death in these diseases; the gross and microscopic appearance of the lesions in the lungs, bronchi and bronchioles with the occasional production of interstitial pneumonias and the frequent bronchiectases. It is common knowledge that one of the important etiologic factors of bronchiectasis is measles. And those who perform necropsies in cases with antecedent influenza histories are forcibly impressed with the frequency of the irregular fusiform and saccular dilatations of the bronchi and bronchioles. (In this connection it will be interesting to follow up the cases of influenza leading to convalescence and see the frequency of chronic bronchiectases that will reveal themselves later.) Just as measles predisposes the individual to secondary invasions of the respiratory tract, as a result of pathologic changes occurring in the epithelium of the tracheobronchial tree, so also it would seem that influenza produces not unlike changes which greatly facilitate secondary invasion by organisms such as the streptococcus, pneumococcus or *B. influenzae*. It seems reasonable to assume that the type of invasion depends to a great extent on the type of organism present in the throats of large numbers of individuals in any given locality. In places where the influenza bacillus is prevalent, this organism will be found in the associated inflammatory conditions. In districts where a certain type of pneumococcus is present, the pneumococcus will be found as the principal invader. In areas where the hemolytic streptococcus is the inhabitant of the throat in a large percentage of the patients, the hemolytic streptococcus will be found in the lungs, pleural cavities and other organs or tissues of the body.

While carrying on investigations in this laboratory on the spread of diphtheria by means of the hands and fomites,[1] the results suggest that the rapid spread of influenza may, to a very large degree, be due to extensive contamination of the hands and fomites with the virus. This contamination is due to the fact that nearly all the cases of influenza present more or less pharyngeal involvement and coryza; conditions which necessitate the frequent use of handkerchiefs, and these consequently soon become saturated with the secretions. Thus the hands of the patients remain persistently contaminated—a condition which even the rigid discipline of the doctors and nurses cannot prevent. There is practically no disease, with the exception of the "com-

1. Barron, M., and Bigelow, G. H.: Diphtheria at a Hospital Center, J. Infect. Dis. **25**:58 (July) 1919.

mon colds," which has a greater chance of perpetuating an almost continuous state of contamination of the hands than does influenza during the early, acute stage of the disease.

The study of influenza at this center emphasizes the fact that the etiology of this disease is as yet unknown. The great diversity of findings in different laboratories throughout the world makes it reasonable to assume that a filtrable virus is most probably the etiologic factor. This organism, whatever it may be, would produce in most cases only a self-limited disease were it not complicated by the secondary invaders such as *Streptococcus hemolyticus,* pneumococcus or *B. influenzae.* This invasion is consequent to a lowering of the barrier in the epithelium of the respiratory tract by this unknown agent. The disease is spread by nasal and pharyngeal secretions and probably also through the conjunctivae. Hands and fomites probably play a very important rôle. It would seem that from a clinical standpoint effort should be directed, for the present at least, not so much to prevent the spread of influenza, which is so difficult, but to prevent the entrance of the secondary invaders which nearly always are responsible for the seriousness of the disease and for death, when the latter occurs.

NEPHRITIS

Acute parenchymatous changes of the kidneys were relatively frequent, occurring in about one fifth of the cases. However, about one half of these cases were very mild. Fairly definite lesions were present in about 11 per cent. of all cases. No characteristic gross kidney lesions were noted in cases of uncomplicated gaseous gangrene. Lesions sufficiently pronounced to cause death were encountered only twice, or in 0.6 per cent. It was gratifying to note how very few definitely chronic lesions of any kind had escaped the observation of the Army examining boards when recruiting was in progress.

PERITONITIS

Peritonitis was encountered forty-one times. Of the thirty-seven cases of acute peritonitis, twelve were attributable directly to gunshot wounds. Several of these patients were definitely not transportable and died soon after their admission to the hospital. One case of peritonitis had an unusual and obscure etiology. There was found a complete rupture of the ileum a short distance above the ileocecal valve. The intestine was completely severed as if by a pair of scissors. The ends were black and necrotic for a distance of a few millimeters. The healthy portion of the intestinal wall stopped abruptly. The mesentery opposite the rupture was thickened and indurated. On the superior

surface, at a point 2 cm. above the intestinal attachment, there was an ulcer, 15 mm. in diameter and 5 mm. in depth, involving a lymph node. The base and walls were necrotic and covered with purulent exudate. The upper surface of the intestinal coil had curled upward, plastering itself firmly to the mesentery and covering the lower margin of the ulcer. It apparently was Nature's vain attempt to prevent the rupture of the suppurating lymph node into the peritoneal cavity. On the inferior surface of the mesentery opposite this ulcer there were strong fibrous adhesions binding the mesentery to the brim of the pelvis. The rupture of the intestine probably resulted from this inflammation and ulceration, completely cutting off the blood supply of one small segment with the resulting rupture. The cause of the suppuration of the lymph node could not be determined.

GAS INHALATION

Of the patients who died, 10.9 per cent. gave a history of gassing. Nearly all were cases of mustard gas inhalation and contact. The pathology of these cases was studied in greater detail by a member of the Central Laboratory staff.[2] All gradations of lesions were found, from acute congestion of the mucosa covered by a thin fibrinopurulent exudate to that of a severe fibrinopurulent tracheobronchitis with ulceration. The most advanced cases presented numerous ulcers through the mucosa of the trachea and bronchi with extensive destruction of tracheal cartilages. There were large areas of gangrene with abscess formation in the lung. Nearly all of the advanced cases showed abscesses and gangrene of the lungs. The exudate in the larynx was generally very pronounced, and often diphtherial in appearance, so that on several occasions there resulted confusion in diagnosis.[1] The complicating pneumonia was always of the bronchogenic type. Hemorrhages into the lungs were common.

PULMONARY TUBERCULOSIS

Of the thirty-six patients (10.1 per cent.) showing pulmonary tuberculosis, 66⅔ per cent. had chronic or healed lesions. These presented simply old scars or fibrosed nodules at the apices, most often on the right. Caseating and calcareous nodules were sometimes present. Of the twelve cases of acute, or acute and chronic, tuberculosis, only a few had lesions extensive enough to be factors in the final exitus. In practically no case could tuberculosis be assigned as the primary cause of death.

2. Covey: Pathology of Mustard Gas Inhalation, Am. J. M. Sc. **157**:808 (June) 1919.

SEPTICEMIA

Nine per cent. of all cases had gross evidences of septicemia at necropsy in conjunction with antemortem as well as postmortem positive blood cultures. Three fourths of the cases were due to *Streptococcus hemolyticus*. The most constant findings in these cases were extensive jaundice of the skin and conjunctivae, together with subepicardial and subpleural petechial hemorrhages.

MENINGITIS

Altogether, twenty-two cases of meningitis came to necropsy. Exactly one half of these were meningococcic in origin. The mortality of this form of meningitis was very unsatisfactory in spite of the energetic treatment with large quantities of serum.[3] Three cases were due to pneumococci, two of which occurred with an initial history of influenza. All three cases were superimposed on pneumonias or empyemas. In one case, the spinal fluid was very turbid, and direct smears of the uncentrifuged specimen revealed the pneumococcus in numbers comparable to those found in twenty-four-hour cultures. Typing revealed the pneumococcus to belong to Group II.

There was one case of tuberculous meningitis. The diagnosis was made shortly before death by finding tubercle bacilli in the fluid. At necropsy, there was found, in addition to the advanced meningitis, tuberculosis of the kidneys and bladder and tuberculous caries of the eleventh dorsal vertebra. Nothing but a shell of the body of the vertebra remained. This was wholly unsuspected, since it had given no clinical symptoms.

The seven other cases in the series were mostly streptococcal, and were consequent to traumatic lesions of the brain and spinal cord.

ANEMIA FROM HEMORRHAGE

Severe secondary anemias, sufficient to produce symptoms and death, were found in 4.5 per cent. of the cases. In a few of these, the anemias were complicated by septicemias. The majority of the uncontrollable hemorrhages followed ruptures, through gunshot wounds, of the femoral and gluteal blood vessels. One patient died of hemorrhage from the internal maxillary artery which continued to bleed even after the common carotid on that side had been ligated.

GAS GANGRENE

Gas gangrene was present in fifteen cases. When the organism was identified, it nearly always proved to be the *B. welchii*. In no case was

3. Bigelow: Nonepidemic Epidemic Meningitis, Arch. Int. Med. **23**:723 (June) 1919.

the *B. edematiens* recovered, although several of the cases presented gross lesions—very extensive edema with very little gas in the tissues—characteristic of the bacillus of toxic edema. In antemortem examinations of wound anaerobes, the *B. vibrion septique* was identified in five cultures. The brownish red, dry, very friable, crepitating muscles produced by the *B. welchii* was very characteristic and easily identified.

PERICARDITIS

Pericarditis was present in 3.9 per cent. of the cases. In several cases there was present a purulent or fibrinopurulent exudate to the extent of a liter or more within the pericardial cavity. Yet, with perhaps one or two exceptions, no antemortem diagnoses of the condition were made. It doubtless proved, relatively at least, the greatest diagnostic pitfall.

The chronic pericarditides were of the adhesive type. The chronic "patchy" epicarditis—the so-called "soldier spots" of some writers—were very interesting because of their frequency. Unfortunately, they were so common, that not sufficient attention was paid to them. They were encountered many times more frequently than in civil life. Many stages in their development could be traced out. There were some with a patch about 2 cm. in diameter situated over the right ventricle anteriorly, several centimeters above the apex. From this patch, a bundle of white, coarse adhesions, 2 cm. in length, extended, uniting it with the corresponding surface of the pericardial wall. The next stage found was where the adhesions were already ruptured showing a large tuft of adhesions hanging free from the epicardium and a smaller tuft of adhesions projecting from the pericardial sac. The next stage showed a rough, thickened epicardial patch with no or only a few very short tags present. The corresponding surface on the pericardium showed slight evidences of adhesions or thickening. The last stage showed a simple, opaque, glistening, white, thickened patch of the epicardium. There were no more evidences of any lesions on the corresponding point of the epicardium.

ENTEROCOLITIS

Twelve, or 3.3 per cent., of the cases showed lesions in the large and small intestines other than those resulting from typhoid fever. Of these twelve cases, three were due to *Endameba dysenteriae* in which the parasites were demonstrated in preparations made from the ulcers. Two cases presented classical pictures of bacillary dysentery. The involvement was principally in the colon, but extended also for a considerable distance up into the ileum. The crests of the folds of

mucous membrane were covered with thick, dull layers of exudate. The mucosa was edematous and hemorrhagic. Numerous ulcers were present which in some areas were so extensive as to leave only islands of polypoid patches of mucous membrane. Cultures were taken from the feces and heart's blood, but not from the spleen or mesenteric lymph nodes, and this may account for the negative bacteriologic evidences for the identification of the lesions. Seven cases had extensive lesions in which neither endamebae nor *B. dysenteriae* were demonstrated, and the gross pictures of the ulcerations were not sufficiently characteristic to make a definite diagnosis. Not a single case of *B. dysenteriae* of any type was isolated at this center, although numerous cultures were made of suspected stools. Typhoid and paratyphoid organisms were occasionally isolated both from the feces and from the urine, as well as from necropsy material.

ZENKER'S DEGENERATION

Parenchymatous degeneration of the recti muscles with hemorrhage and rupture was strikingly frequent. Several of the cases were frank cases of "Zenker's" degeneration, both grossly and microscopically. The others showed the swelling of the muscle fibers, the hemorrhage and rupture of the muscle bundles, but the yellowish "waxy" appearing areas were not so prominent grossly.

Seven of the nine cases were associated with pneumonia following a history of influenza. In one of these there was also present a hemorrhagic encephalitis. Of the two remaining cases, one was associated with pneumonia complicating gunshot wound, and the other with pneumonia in which the initial diagnosis was not stated. Not a single case of typhoid presented this lesion, although typhoid is considered in the textbooks as being the principal disease in which it is found.

Several interesting confusing diagnoses resulted from the hemorrhage and rupture of the abdominal rectus muscles. In one case a diagnosis of appendicitis was made which was fortunately treated medically and not surgically. At the necropsy the appendix was found to be normal, but the lower third of the right rectus muscle showed typical Zenker's degeneration with rupture. In another case, the patient suddenly developed signs of acute cholecystitis. All his symptoms were referred to the gallbladder region. There was marked tenderness, severe pain, some rigidity and a distinct mass was palpable. An area of dulness the size of an orange, in the region of the gallbladder, was outlined. The findings were so definite that it was decided to operate, but not until a careful consultation was held. A diagnosis of acute cholecystitis, probably suppurative, was made. On the day set for operation, the patient developed edema of the lungs and sank into a

condition too serious for operation. He died several days later. At necropsy, the gallbladder was found to be entirely normal, and this time the upper right rectus muscle showed Zenker's degeneration with rupture and extensive hemorrhage into the sheaths which extended upward to the insertions at the costal cartilages. The greatest amount of blood clot was found just below the costal margin.

One point of differential diagnosis between these lesions in the rectus muscles and true surgical conditions within the peritoneal cavity was brought out at a discussion in one of the clinicopathologic conferences. Whereas tenderness and pain is elicited readily by very superficial palpation in the first instance, it is only on deeper palpation that the maximum discomfort is produced in the latter case.

TYPHOID FEVER

In this series eight cases of typhoid fever were encountered. Only one or two were diagnosed clinically. The lesions in the intestines were characteristic, but extensive ulcerations in the colon were more frequently encountered than is the usual experience. In most of the cases, the *B. typhosus* was recovered from the spleen, gallbladder and the heart's blood. A few cases failed to give any bacteriologic evidences of the disease although the gross lesions were definitely diagnostic.

The clinical diagnosis of typhoid and paratyphoid fever proved quite a problem. In many cases at the center which were clinically typhoid, no corroborative laboratory evidences could be obtained either in positive blood cultures or in positive stool or urine cultures. The ordinary Widal test is, of course, worthless in prophylacticated individuals. One of the laboratory staff[4] obtained interesting results by using Dryer's quantitive agglutination, which promises to be a valuable aid in differential diagnosis of this disease in prophylacticated individuals, where cultural evidences are negative. No known case of paratyphoid fever came to necropsy.

DIPHTHERIA

The mortality from diphtheria was very disappointing. Several patients dying of diphtheria came to necropsy with the case undiagnosed clinically. The reasons for this are discussed fully by Barron and Bigelow.[1] All cases were of the laryngeal type — a condition rather unusual for adults.

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4. Eggerth: A Study of Dreyer's Agglutination Technique in the Army, J. Infect. Dis., 1919 (in press).

HEMORRHAGIC ENCEPHALITIS

Three cases of hemorrhagic encephalitis are included in the series. One case was associated with ascending myelitis associated with complete transverse laceration of the lower dorsal cord following gunshot injury. Another case was associated with pneumonia following a history of influenza. The third case was associated with a beginning bronchopneumonia in a patient who had apparently completely recovered from a gunshot wound. The patient was ready for evacuation when he became sick very suddenly with a high temperature, rapid pulse and increased respiration. The next morning after his readmission to the hospital, a diagnosis of lobar pneumonia was made. Shortly afterward, he developed symptoms of increased intracranial pressure, with subnormal temperature, pulse 46, respiration 8. Retinoscopy revealed a "choked disc." He died less than forty-eight hours after admission. At necropsy there was extreme injection of the pia mater and the arachnoid membrane. Section of the brain showed the white matter peppered with pinpoint to pinhead sized hemorrhages most marked in the corpus striatum on the left side, the corpus callosum and in the pons. The lungs showed only the very earliest stage of bronchopneumonia. The blood culture made at necropsy was sterile. Unfortunately no cultures were made from the brain tissue.

CONGENITAL ANOMALIES

Of the fourteen prominent congenital anomalies, exactly 50 per cent. involved the kidneys. There were three cases of horseshoe kidney. Two cases of hypoplasia were found in which the involved kidneys were about the size of lima beans, while the kidneys on the opposite side were about twice the normal size, a compensatory hyperplasia. There were two cases of complete aplasia of one of the kidneys. In these, not only was there no vestige of kidney substance found, but there was not a trace of the corresponding ureter.

Of the remaining anomalies, only one other is worthy of mention, that of an accessory lung. A mass of tissue entirely covered with pleura, having the size, shape, appearance and consistency of one of the lobes of a lung in a full term fetus, was found in the left pleural cavity attached by a narrow pedicle of connective tissue to the anterolateral prevertebral tissue in the region of the eighth dorsal vertebra. This pedicle appeared like the structure of the hilus of a lung, but had no relation to any of the structures of the normal lung. The only connection discovered between it and the normal structures was through two arteries, each about 2 mm. in diameter (outside), arising from the aorta in that region. These arteries were, of course, entirely

anomalous. The parenchyma did not crepitate and contained no air. On section, a miniature bronchial tree could be identified in which the structure corresponding to a bronchus measuring about 5 mm. in diameter ended blindly and bluntly in the loose cellular tissue of the "hilus" near the two arteries. Microscopically, the tissue shows definite bronchial and bronchiolar structure, with cartilages, nonstriated muscle fibers and connective tissue. The blood vessels are prominent. The lumen is lined with a high columnar epithelium and contains mucoid material mixed with epithelial cells and other cellular debris. The parenchyma shows a rather loose cellular connective tissue through which are scattered islands of cuboidal and columnar epithelial cells, some thrown together irregularly, others arranged in gland-like structures. This tissue will probably be studied more in detail by me at some future time.

SUMMARY

A number of important facts reveal themselves in the study of this material. A few of them are the following:

Empyemas and acute pericarditides are not so readily diagnosed as the textbooks would make one believe. These conditions have proven pitfalls for some of our best diagnosticians.

A very large percentage of the pneumonia cases have associated suppurative conditions in one or more of the sinuses in the skull. These present very meager, if any, clinical evidences, and nearly always remain undiagnosed until the postmortem examination.

Influenza practically never kills by itself alone. In the present series, pneumonia was the cause of death in nearly all of the cases, a few patients dying of meningitis, typhoid fever, etc. *B. influenzae* of Pfeiffer played no important rôle.

Of all the deaths, about 75 per cent. were medical. Although almost 40 per cent. of the deaths occurred in wounded persons; in a considerable proportion of these the wounds were far too slight to play any important part in causing death.

The surgical treatment of gunshot wounds was at times not sufficiently intensive. Cases came to necropsy which probably might have been saved by amputation of an involved extremity, or by more radical debridement.

Some surgical cases with gunshot injuries to the abdomen were evacuated to base hospitals while in a nontransportable condition.

Zenker's degeneration, with rupture and hemorrhage, is associated with highly virulent infections. It sometimes may cause confusion in diagnosis from intra-abdominal surgical conditions.

Congenital anomalies were present in about 4 per cent. of the cases, and one-half of these involved the kidneys.

Practically no well established chronic lesions escaped the detection of the recruiting medical examining boards.

RÉSUMÉ OF THREE HUNDRED AND FIFTY-SIX NECROPSIES

Statistical Data Up to Jan. 1, 1919

GENERAL CONSIDERATIONS

Total number of patients treated	29,196
Total number of deaths	429
Mortality rate	1.47 per cent.
Total number of necropsies	356

	Patients Treated*	No. of Deaths	Mortality Rate, %	No. of Necropsies
Evacuation Hospital 19	4,951	7	0.14	7
Base Hospital 26	5,512	99	1.79	85
Base Hospital 25	5,860	117	1.99	97
Base Hospital 49	4,626	84	1.81	76
Base Hospital 56	7,766	82	1.05	67
Base Hospital 70	5,371	40	0.78	24

Date of first convoy of patients to center	July 23, 1918
Date of first necropsy	July 26, 1918

NECROPSY FINDINGS

Empyema and pleurisy	225 cases	or 63.2%
Acute pleurisy	95 cases	or 26.7%
Empyema	50 cases	or 14.0%
Chronic pleurisy	50 cases	or 14.0%
Chronic and acute pleurisy	30 cases	or 8.5%
Pneumonia	218 cases	or 61.2%
Bronchopneumonia	165 cases	or 75.5%
Streptococcic	64 cases	or 38.8%
Pneumococcic	20 cases	or 12.1%
Undetermined	81 cases	or 49.1%
Lobar pneumonia	37 cases	or 17.0%
Pneumococcic	16 cases	or 43.2%
Streptococcic	11 cases	or 29.8%
Undetermined	10 cases	or 27.0%
Interstitial	16 cases	or 7.5%
Streptococcic	16 cases	or 100 %
Positive blood cultures	163 cases	or 45.8%
Hemolytic streptococcus	84 times	or 51.4%
Nonhemolytic streptococcus	35 times	or 21.3%
Pneumococcus	26 times	or 16.0%
B. welchii	12 times	or 7.3%
B. pyocyaneus	5 times	or 3.4%
Staphylococcus	1 time	or 0.6%
Number of wounded	142	or 39.8%
Parts wounded	163	
Extremities	86	or 52.7%
Abdomen	28	or 17.1%
Chest	26	or 16.0%
Head	23	or 14.2%

* This total includes 4,890 patients received by transfer.

Number of bones fractured	91	
Ribs	13	
Femur	12	
Ilium	10	
Vertebrae	10	
Skull	9	
Tibia	7	
Fibula	4	
Scapula	4	
Humerus	3	
Coccix	3	
Radius	3	
Ulna	3	
Ischium	3	
Metacarpal	2	
Sacrum	2	
Ankle	1	
Clavicle	1	
Jaw	1	
Number of cases with otitis media and sinusitis	120	or 33.7%
Number of otitis media and sinusitis involvements	192	
Sphenoidal sinusitis	92 times	or 25.8%
Frontal sinusitis	34 times	or 9.5%
Ethmoidal sinusitis	35 times	or 9.8%
Otitis media	31 times	or 8.7%
Influenza	87 cases	or 24.4%
Pneumonia following influenza	75 cases	or 36.2%
Bronchopneumonia	48 cases	or 64%
Streptococcic	22 cases	or 45.8%
Pneumococcic	14 cases	or 29.2%
Undetermined	12 cases	or 25.0%
Lobar pneumonia	18 cases	or 24%
Pneumococcic	12 cases	or 67%
Streptococcic	4 cases	or 22%
Undetermined	2 cases	or 11%
Interstitial pneumonia	9 cases	or 12%
Streptococcic	9 cases	or 100 %
Number of cases with otitis media and sinusitis	50	or 57.4%
Number of otitis media and sinusitis involvements	91	
Sphenoidal sinusitis	35 times	or 70.0%
Ethmoidal sinusitis	22 times	or 44.0%
Frontal sinusitis	17 times	or 34.0%
Otitis media	17 times	or 34.0%
Pleurisy	33 cases	or 37.9%
Empyema	13 cases	or 15.0%
Meningitis	7 cases	or 8.0%
Meningococcic	4 cases	or 57.1%
Pneumococcic	2 cases	or 28.6%
Tuberculous	1 case	or 14.3%
Zenker's Degeneration	7 cases	or 8.0%
Pulmonary tuberculosis	4 cases	or 4.6%
Septicemia	5 cases	or 5.8%
Lung abscess	4 cases	or 4.6%
Pericarditis	3 cases	or 3.4%
Typhoid fever	3 cases	or 3.4%
Diphtheria	3 cases	or 3.4%
Mediastinal abscess	1 case	or 1.2%
Encephalitis, hemorrhagic	1 case	or 1.2%
Abscess of kidney	1 case	or 1.2%
Nephritis	76 cases	or 21.3%
Mild	34 cases	or 9.5%
Moderate	40 cases	or 11.2%
Severe	2 cases	or 0.6%

Peritonitis	41 cases	or 11.5%
Acute	37 cases	or 90.0%
Peritonitis from gunshot wound	12 cases	
Chronic	4 cases	or 10.0%
Gas Inhalation and Contact	39 cases	or 10.9%
Tracheobronchitis and pneumonia	26 cases	or 66.6%
Tracheobronchitis	10 cases	or 25.6%
Pneumonia	3 cases	or 7.8%
Tuberculosis, pulmonary	36 cases	or 10.1%
Chronic or healed	24 cases	or 66.7%
Acute	8 cases	or 22.2%
Chronic and acute	4 cases	or 11.1%
Septicemia	32 cases	or 9.0%
Streptococcus hemolyticus	24 cases	or 75.0%
Streptococcus, nonhemolyticus	7 cases	or 21.9%
Streptococcus viridans	1 case	or 3.1%
Meningitis	22 cases	or 6.1%
Meningococcic	11 cases	or 50.0%
Pneumococcic	3 cases	or 13.6%
Tuberculous	1 case	or 4.5%
Other types	7 cases	or 31.9%
Anemia from hemorrhage	16 cases	or 4.5%
Gas gangrene	15 cases	or 4.2%
Pericarditis	14 cases	or 3.9%
Acute	9 cases	or 64.3%
Chronic	3 cases	or 35.7%
Enterocolitis	12 cases	or 3.3%
Amebic	3 cases	or 25.0%
Bacillary	2 cases	or 16.7%
Undetermined	7 cases	or 58.3%
Zenker's degeneration	9 cases	or 2.5%
Typhoid fever	8 cases	or 2.2%
Diphtheria	8 cases	or 2.2%
Hemorrhagic encephalitis	3 cases	or 0.8%
Congenital anomalies	14 cases	or 3.9%
Kidney, horseshoe	3 cases	or 21.4%
Kidney hypoplasia	2 cases	or 14.3%
Kidney aplasia	2 cases	or 14.3%
Patent foramen ovale	3 cases	or 21.4%
Accessory lung	1 case	or 7.1%
Accessory pancreas	1 case	or 7.1%
Pectoral muscle, aplasia	1 case	or 7.1%
Meckel's diverticulum	1 case	or 7.1%

THE POSSIBILITIES OF PHYSICAL DEVELOPMENT IN CASES OF EFFORT SYNDROME BY MEANS OF GRADED EXERCISES*

BERTNARD SMITH, M.D.
LOS ANGELES

Patients who show the "effort syndrome" symptom complex often have a lessened muscular strength in addition to the neurosis that is generally present. This weakness may be limited to a few muscle groups, but it is usually general and may be very marked. This was true with the men who entered this hospital from the American camps during the summer of 1918 and, because of this picture of poor muscular development, graded exercises were among the first methods adopted for an intensive study of the effort syndrome condition. Lewis and his co-workers[1] have used grouped exercises, requiring varying degrees of effort, in estimating the future military usefulness of these men, and, from the results, those men unfit for military service were listed earlier for discharge and the individuals retained in service were classified for duty by the grade of graduate work they could successfully carry through.

In the studies at Lakewood all effort syndrome cases on the cardiovascular wards were admitted to the exercise classes, even though the severity and persistence of the symptoms indicated a definite unfitness for any military service. In trying various forms of exercises, it was found that the confidence of the men in their ability to carry on must be secured and maintained before any efforts toward improved strength could be successful. Sharp, abrupt commands were destructive to this confidence and caused a return of overwhelming symptoms as easily as too severe work. After considerable experiment in arranging exercises for so general a reconstructive problem, the "unit system" was adopted.[2] The eight "units" include all muscle groups and their order is the same in each exercise grade. This report is concerned with the results from these exercises in the attempt to overcome the existing physical weakness.

An estimation of the total strength of each patient was made when he entered the hospital, and again when he was ready for discharge

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* Report from studies made on the Cardiovascular Service, U. S. Army General Hospital No. 9, Lakewood, N. J.

* Read before the Section on Practice of Medicine at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

1. Report of Medical Research Committee, Series No. 8, 1917.
2. Smith, Bertnard: J. A. M. A. **72**:103 (Jan. 11) 1919.

or had completed the highest exercise grade. For these estimations the spring balance resistance test of Dr. E. G. Martin was used, the technic of which is briefly described at the end of this report. Figures for the strength of normal men in active military service were obtained from tests made on one hundred men at Camp Dix, N. J. These men had had a period of full, hard training covering from ten to fourteen months, which they had completed without symptoms. The range and average of these normal estimations are given in Table 1. It was evident from the normal figures obtained that the weight is an important factor if a comparison of strengths is to be made. Consequently, all tests have been computed for total strength (Str.) and for the ratio of strength to weight (Str./Wt.).

TABLE 1.—Strength Estimations on 100 Normal Men in Active Military Service *

Range				Average			
Strength	Weight	Str./Wt.	Age	Strength	Weight	Str./Wt.	Age
1390-2830	54.6-88.5	23.2-30.9	19-40	1655	67.6	25.6	24.1

* All figures for strength and weight are in kilograms.

The clinical history of cases of effort syndrome among soldiers may show that the condition was present previous to entrance into military service. Others give equally definite evidence that the symptoms have developed during the period of active duty. It will be convenient to arrange the cases here reported under these two groups, according to the onset and duration of the general symptoms.

1. CASES WITH SYMPTOMS BEFORE MILITARY SERVICE

Of the 300 effort syndrome cases here reported, 56 per cent. give a history of symptoms having been experienced for a number of years before entrance into the army. The majority of these men have performed very little, if any, real active duty. They have found their way into a hospital or infirmary soon after induction into service.

1. *Type of Intelligence Defect.*—Among the men who give a history of this long duration of symptoms, thirty-five showed definite but varying degrees of defective intelligence.[3] These give differentiating characteristics that deserve attention. They are lacking in both physical and mental drive, and can be neither persuaded nor forced to do their full part in training. They have a persistently poor coordination, and go through the work of the various exercise grades with joints sagging and muscles relaxed. These men are without ambition and show a stubborn resistance to any effort that is made to change them

3. Campbell, C. Macfie: J. A. M. A. **71**:1621 (Nov. 16) 1918.

from the low economic level to which they have become adapted. Their ability to adjust themselves to a new environment, especially to military conditions, is slow and limited. The physical weakness may be extreme (Table 2), but this is not constant, and the less severe cases may have a strength that is very near normal.

TABLE 2.—Comparative Strengths of Cases of Effort Syndrome Before and After Exercise

	No.	On Entrance to Ward			On Discharge from Ward		
		Range of Str.	Range of Str./Wt.	Average Str./Wt.	Range of Str.	Range of Str./Wt.	Average Str./Wt.
Symptoms of long duration:							
1. Intelligence defect	35	175-1870	3.9-24.4	15.1	780-2006	10.7-28.0	21.5
2. Physical invalidism	110	344-1475	6.7-22.8	14.8	883-2061	15.3-36.3	24.8
3. Unclassified	23	492-1619	10.8-34.0	21.0	1154-1420	18.9-26.0	23.3
Symptoms recent:							
1. After strain	70	600-1961	9.0-26.0	20.4	1225-2180	22.2-37.6	26.9
2. After infections*	62	593-1621	9.7-28.2	19.3	1249-1944	19.3-31.9	25.8
After rheumatic fever†	33	822-1706	15.3-27.4	21.3	995-2105	18.6-29.8	25.4

* Not including cases following rheumatic fever.
† Not included in cases of effort syndrome.

Satisfactory strength estimations are often difficult to obtain in severe cases of the defective intelligence type because of the lack of cooperation. Consequently, it is doubtful if the low figures represent true strength values. In Chart 1 curves are given which show variations in strength estimations made at three periods of the same day, both at the time of entrance into the hospital and at the time of discharge. The ten curves are from estimations made on men of the defective intelligence type who had low strength readings. At the time the first observations were made the day was spent quietly on the wards or with the various routine examinations. The second group of curves are from tests made after two or more months had been spent in daily exercise classes and when the day was well occupied with educational or vocational work, together with the classes in physical training. There is a general gain in strength, but the type of curve persists. Curves obtained in the same way from the normals and from other types of effort syndrome cases are of no constant form. Ryan tests[4] on this type of constitutional inferiority show an early fatigue. While these ndividuals can advance through the exercise grades with but few symptoms and with some slight gain in general strength, the fact that they will always put the least amount of effort possible into the work is probably explanatory of the early, persistent fatigue. With the gain in general strength there is a betterment of the general health, but the mental sluggishness remains unchanged and

4. King, John T., Jr.: Arch. Int. Med. **23**:527 (April) 1919.

the men will not make any independent effort to avoid slipping back into the former condition.

2. *Type of Chronic Physical Invalidism.*—The majority of the men whose symptoms have persisted for a long time give a picture that is in rather sharp contrast to the type just considered. Here the physical weakness forms the predominant and constant picture. These men

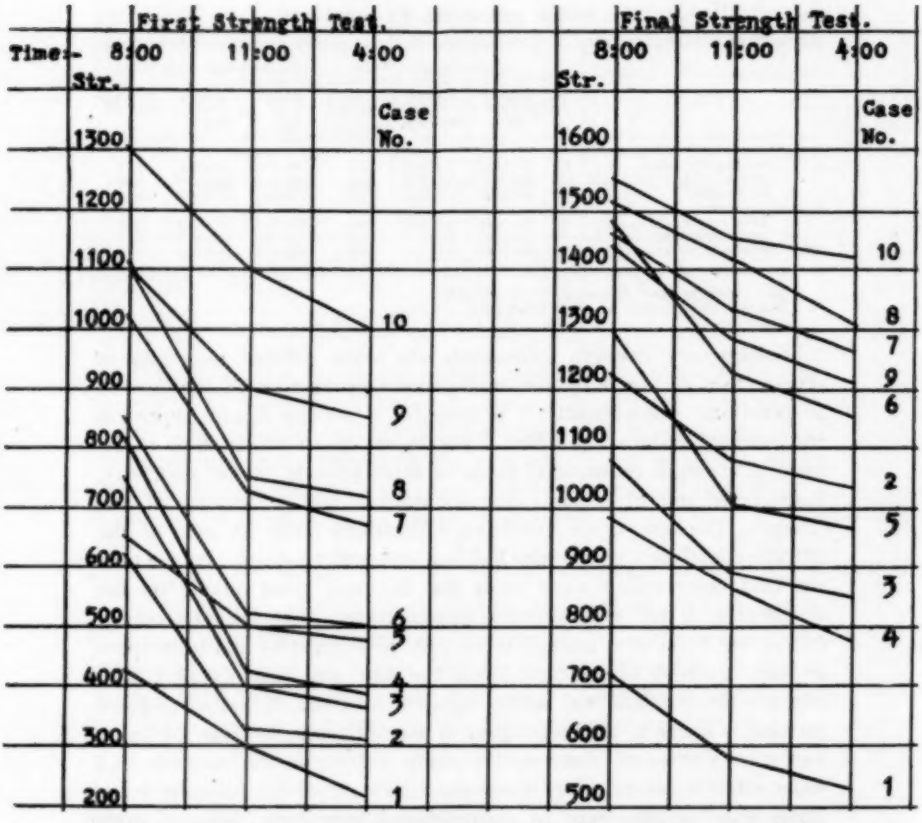

Chart 1.—Fatigue curves in severe cases of effort syndrome. Defective intelligence type. Curves from estimations of strength made before and after work in graded exercises.

have "never been strong," or trace the beginning of the trouble to an illness in early life, frequently in infancy or childhood. A diagnosis of serious heart trouble, combined with the watchfulness of over-solicitous parents, form important contributing factors. The patients have learned to interpret the symptoms that appear after physical exertion as warnings of serious overstrain.

Since the fear of the results of this overstrain has become very magnified, it is important that physical training for these men should begin with exercises of so mild a form that no symptoms result. Advancement in the graded work must be slow and so well graduated, especially in the lower classes, that the individual is not too conscious of the increased effort demanded. Some symptoms may be experienced on beginning a higher grade which will disappear after two or three days of perseverance. Men of this type usually have a normal mentality, and such cases can be found among college and university students. Some manifestations of neurosis are usually seen in these men, but this factor is usually subordinate to the physical weakness. However, progress in the exercises may depend more on the ease with which self-confidence can be developed and maintained than on the general strength present at the beginning of the work. The man with the lowest strength of 334 kg. (Table 2) returned to duty at the end of two months, having completed all the exercise grades with a final strength of 1,658 kg. These men differ from the cases with defective intelligence, in that their cooperation is complete as soon as confidence in their own ability to carry on is restored. After they are able to take part in the more vigorous games and exercises, future progress is usually secure. The pride in their increased strength and their joy in losing the stigmata of being a weakling are sufficient to carry them ahead and should prevent them from falling back into old habits.

In the cases here reported, 110, or 37 per cent., belong to this type of physical inferiority. Of these, 84 per cent. advanced into the fifth grade of exercises in an average time of 10.6 weeks, and took part in active athletic games. The figures in Table 3 that represent the men who only reached the third and fourth grades should not be interpreted as meaning a permanent limit for these individuals. These grades were their limit only for the time they were in the hospital. Proper training after discharge should secure further improvement.

A special exercise class was formed with twenty-five patients selected from the group where symptoms were of long duration, with the desire to test the results of a more intensive training under close supervision. These men began with various forms of track work and athletic games, in addition to heavier exercises than those in the regular work for lower grades. The results with fifteen men of the chronic invalidism type are given in Table 4. The average ratio of strength to weight (Str./Wt.) on beginning work in this special class was 15.0, and, after an average of ten weeks of training, this ratio had increased to 23.6. With the 110 men who had their training in the general classes, the first strength to weight ratio averages 14.8. After an average of 10.6 weeks of work this ratio average had increased to

24.8. In the more intensive work it was definitely more difficult for the men to maintain the degree of effort required without becoming too conscious of the general effort syndrome symptoms.

TABLE 3.—Time in Exercises of Effort Syndrome Types, with Final Grade Reached

Type*		No.	Weeks in Exercises		Final Grade at Time of Discharge, with Average Str./Wt.											
					Grade I		Grade II		Grade III		Grade IV		Grade V		Grade VI	
			Range	Average	No.	Str./Wt.	No.	Str./Wt.	No.	Str./Wt.	No.	Str./Wt.	No.	Str./Wt.	No.	Str./Wt.
III	1	35	10-19	12.5	1	10.7	2	14.6	2	15.4	6	17.2	9	22.4	15	25.3
	2	110	9-16	10.6	0	....	0	....	3	16.2	15	18.6	42	24.1	50	26.4
	3	23	8-13	10.5	0	....	0	....	0	....	4	19.3	10	24.4	9	25.8
II	1	70	5-13	8.4	0	....	0	....	0	....	0	....	5	24.8	65	25.5
	2	62	8-12	9.3	0	....	0	....	1	19.4	5	21.1	14	24.8	42	25.6
After R. F.		33	7-13	8.6	0	....	0	....	0	....	4	19.8	16	24.1	13	25.2

* Group and type numbers correspond to those in Table 2.

TABLE 4.—Results of Intensive Training in Cases of Chronic Invalidism Type

Name	First Str.	First Str./Wt.	Weeks in Class	Final Str.	Final Str./Wt.
R. F.	1006	16.7	9	1240	20.6
F. W.	1033	18.8	9	1250	22.7
G. H. D.	757	12.8	12	1450	24.6
G. L.	1499	21.0	11	1881	25.7
E. M.	1141	18.2	8	1628	25.2
E. J. G.	689	12.5	12	1215	22.0
H. R.	972	14.8	9	1588	25.6
G. H.	830	13.3	8	1678	26.9
C. H.	1175	18.2	10	1445	23.9
F. P.	441	8.0	12	1022	18.5
R. D.	830	18.5	19	1220	23.5
O. S.	842	14.3	10	1365	23.1
S. G.	791	12.7	10	1334	21.6
W. H.	1335	20.4	13	1820	27.7
W. E. H.	218	4.3	9	1332	22.6
Average	903.7	15.0	9.9	1431.7	23.6

3. *Unclassified Type.*—In Tables 2 and 3 cases are included under "unclassified type" that had predominating nervous symptoms. Some degree of neurosis is present in all effort syndrome cases and must be recognized in a successful treatment of this condition. But there were a few men whose progress in graded work was so controlled by the nervous factor that they deserve a separate grouping. Frequent fainting attacks, complaint of severe dizziness, independent of exertion and other indications of a marked nervous instability separate these men from the other types and limit their advancement in the exercises. The general strength shows a wide variation, and there is usually no indica-

tion of a defective intelligence. These men require neuropsychiatric attention in addition to the physical training.

II. CASES DEVELOPING SYMPTOMS DURING MILITARY SERVICE

As the period of active fighting for our troops continued, the type of cases admitted to the wards with the official diagnosis of cardiac disorder functional changed from the group with long continued symptoms to men with a greater strength in whom the condition had developed during active army duty. These patients have a previous history that is negative for the usual effort syndrome symptoms. The symptoms they present on entrance to the hospital may differ in no way from those of the more chronic group.

1. *After Nervous and Physical Strain.* — Of the 132 men who belong to this group with a recent onset of symptoms, seventy, or 53 per cent., give no etiology other than the severe nervous and physical strain of military duty. Many of these men were engaged in rather sedentary occupations in civil life, but had always considered themselves well and strong. They went through the period of training in the American camps without difficulty, and only eight of the seventy broke down during the intensive training overseas before being sent to the front. The first strength tests on these men give higher average values than are found in the cases with long continued symptoms. Also the confidence of these men in their ability to get back into condition is not so thoroughly destroyed. Many are able to advance rapidly through the exercise grades and are free from symptoms after four to six weeks of graded work. Of the seventy men, sixty-five completed all the grades of exercises without symptoms in an average time of 8.4 weeks. These men are a much milder type than are those reported by the British workers. It must be remembered that the American troops were in active fighting for a much shorter time.

2. *After Infectious Disease.*—A group of sixty-two men were admitted to the cardiovascular service with a diagnosis of a functional cardiac disorder following some infectious disease. The cardiac symptoms had developed during the convalescence or after the patient had returned to duty. Some of these men were admitted from American camps and were in an earlier stage of convalescence than were the men returned from overseas. This may account, in part, for the lower average strength on admission than was found in the case of the men who broke down under strain. The gain in strength and the disappearance of the symptoms in graded exercises is about equally rapid in these two types. However, some complication may persist in the postinfection cases which limits their advancement in the graded work.

Patients giving a history of symptoms developing after acute rheumatic fever have not been included in this report of effort syndrome cases. The common incidence of rheumatic fever in organic heart disease influenced the separation of these cases into an independent group, even though a thorough study and close observation during a long period of graduated work failed to reveal any organic defect. In Tables 2 and 3 are appended the observations in thirty-three cases in which the men developed symptoms after acute rheumatic fever. It is shown that 88 per cent. of these men advanced into Grade 5 exercises, and 39.5 per cent. completed the highest (6) grade. In cases of the general postinfectious type, 90 per cent. of the men completed Grade 5, and 68 per cent. finished the work of all grades successfully. Men with arthritic symptoms are not included in this postrheumatic number, but among the postinfectious patients, a number had persisting complications. Arrhythmias due to some myocardial defect are more frequently found in the postrheumatic cases during the exercise work, and these men must be advanced in the grades only under the most careful observation.

GENERAL DISCUSSION

The classification used in this report is purposely broad, since the desire is to emphasize the fact that variations in type can occur among cases presenting the effort syndrome symptom complex rather than to advocate any fixed terminology. It is believed that a more rational understanding of this condition can be reached and a more successful treatment carried out when an appreciation of the variations in type is recognized and an individual study of each patient is made.

Men who have presented symptoms for a long period of time, and who have failed to stand up to their earlier military training, cannot be built up to a normal strength in the short time and by the intensive methods necessary during a military emergency. Such treatment will only increase the severity of the symptoms, and the patient is given a more fixed idea of invalidism in consequence. The treatment is more properly a civil problem, and should receive its deserved attention during the time of peace. The importance of recognizing this is emphasized when we consider the number of recruits who were found to be unfit for military service because of a poor physical development unassociated with any organic disease.

Men belonging to the type of chronic physical invalidism have a military value if they can be developed to a condition of greater strength and, what is even more important, they can be made fit to successfully undertake more active work in civil life with an improve-

ment in their economic life. There is an increase in their military value that is, to some degree, in direct proportion to their ability to stand up to more active civil work.

Men showing definite intelligence defect present the most discouraging problem in treatment. The mental sluggishness does not permit of a satisfactory cooperation from these men.

Where the symptoms have been of short duration and acquired during active military duty, the general strength shows a higher average and the men lose their general symptoms more rapidly. This is especially true where the condition follows the physical and nervous strain of front line fighting, and the symptoms are no more persistent than in the cases here reported. If comparisons are to be made, it must be remembered that our troops were not in the fighting line so long as were the allied forces. Also, the signing of the armistice removed any fear of a return to active duty which might have been an important factor in delaying recovery.

Men who develop the effort syndrome after acute infections will improve rapidly in strength and in symptoms through graded exercises. They may be limited in their advancement through the grades by some resulting complication. When carried out under proper supervision, well graded exercises should form an important part in the late treatment of infectious diseases.

No attempt has been made in this report to give the percentages of men returned to duty. It is doubtful if any reached the front line in time to take part in active fighting for a sufficient length of time to be a satisfactory test. A number have been heard from through personal communications, several months after they had returned to civil life, and these report having taken up more active work than had been their former occupations and having been free from symptoms.

All strength estimations included in this report were made with the assistance of Dr. John T. King, Jr., to whom I am indebted for most efficient cooperation. I wish to express my appreciation of the work done by the men who directed the classes in graded exercises: G. J. Altman, Paul M. Krimmel and Morris Kaufman. The general plan adopted for the exercises was worked out by these men and the success of the work was largely due to their able and faithful services.

THE MARTIN STRENGTH TEST

SPECIFICATIONS

First.—A self-registering spring balance and ice scale. A very satisfactory scale is now furnished by John Chatillon and Sons, 85 to 93 Cliff Street, New York City, as "Special Strength Tester. Style No. 100 B." The capacity should be designated in ordering and can be had in pounds (200) or kilograms (100).

Second.—An upright post with a hand hold. A stout post, 4 inches square and 6½ feet high, mounted on a firm base. The post should be smooth and have the corners rounded off. A strong rod, 1½ inches in diameter and 24 inches from the post, should be placed as a hand hold.

Third.—A stout table of ordinary height, not less than 6½ feet long and 2½ feet wide, with a cleat of wood about 2 feet by 1½ inches by 3 inches, securely fastened on the top of the table across one end, with the greater diameter vertical.

PROCEDURE

Ten groups of muscles are tested: 1. Right pectoral; 2. left pectoral; 3. right wrist flexors; 4. left wrist flexors; 5. right forearm flexors; 6. left forearm flexors; 7. right thigh adductors; 8. left thigh adductors; 9. right thigh abductors; 10. left thigh abductors.

After the loop of the balance is adjusted and the subject is in position, the command "hold back" is given. At this command the subject contracts the muscles of the group being tested with all his power and, simultaneously, the operator pulls on the spring balance. The tension must be developed as rapidly as possible, without jerking, and must be increased until the resistance of the subject is entirely overcome.

TECHNIC

Pectoral Groups: The subject stands at attention, with the middle of his back pressed firmly against the upright post, and the hand of the arm not being tested grasping the hand hold. The adjuster stands directly in front of the subject, facing him and places the loop of the balance about the arm to be tested, just above the elbow. With one hand he holds the loop in position and, grasping lightly the hand of the arm to be tested, draws the arm across in front of the subject's body as far as possible, keeping the arm straight and as close to the body as can be done and still give clearance for the loop. At the command "hold back," the subject makes all the resistance possible and the operator develops sufficient tension to draw the arm down to the side of the body. The pull must be discontinued before the arm has been drawn beyond the vertical line.

Wrist Flexors: The subject stands beside the upright post with the arm to be tested so flexed as to bring the forearm horizontal. The back of the forearm must rest against the post, and the hand project beyond the post to the ulnar process. The adjuster stands directly in front of the subject's palm. With one hand he holds the subject's wrist against the post and, with the other, he holds the loop in place. The loop is placed so that its middle is directly over the crease at the base of the fingers. Keeping the fingers straight, the subject's hand is flexed at the wrist. The operator pulls at an angle just less than 90 degrees from the plane of the subject's hand. Tension must stop as soon as the hand begins to yield.

Forearm Flexors: The subject lies on his back on the table, with his heels pressed firmly against the cleat. The adjuster stands at the subject's left for both flexors. His right hand holds the subject's forearm in a position of flexion, about 15 degrees toward the shoulder from the vertical, and places the loop about the wrist so that its upper edge is at the crease in the skin at the base of the hand. The operator stands at the foot of the table. Tension is relieved when the forearm reaches the vertical.

Thigh Adductors: The position of the subject is the same as for the forearm flexors, except that he presses against the cleat with only the foot of the leg that is not being tested. The adjuster stands at the foot of the table. With one hand he places the loop in the hollow just above the malleolus, seizes the subject's heel with the other hand, lifts the leg until the heel is just high enough to clear the other toe, and then draws the leg into extreme adduction. The toe of the leg to be tested must be upright. The operator stands at the side of the table, develops tension at the word of command and draws the leg outward from the side. Tension is relieved as soon as the leg has been drawn into line with the axis of the body.

Thigh Abductors: The positions of the subject and adjuster are the same as in the last test. The loop is adjusted as for the adductors but the pull is in the opposite direction. The leg is drawn out beyond the midline of the body to an angle of about 15 degrees, and the effort of the subject is to prevent the operator from drawing the leg into line with the body. The tension is relieved when the leg reaches the midline.

Calculation.—The sum of the strength shown by these ten groups of muscles constitutes in men 17.7 per cent. of the entire strength as found by this system of testing. To calculate the total strength therefor, the sum of these ten determinations must be multiplied by the reciprocal of 0.177, which is 5.65. The product thus obtained is the figure for the strength of the individual.

NOTE

This technic is printed with the consent of Dr. Ernest G. Martin, to whom I am indebted for permission to use the test. I wish also to express my appreciation of the suggestions regarding the technic that were given by Prof. F. S. Lee.

EXPERIMENTAL EMPHYSEMA*

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IOWA CITY

In the recent epidemic of influenza and bronchopneumonia, among the S. A. T. C. at the Iowa State University, there were about 1,100 cases with thirty-three fatalities. Of these, twenty came to necropsy.

One of the most striking and constantly present postmortem findings in these cases was a marked vesicular and interstitial emphysema. The vesicular emphysema was mainly marginal, but large emphysematous bullae were quite frequently observed subpleurally. The apices of both lungs, especially the upper lobes, were involved. In many cases superficial distended air vesicles ruptured and allowed an escape of air subpleurally, giving the lung a beaded appearance. The roots of the lungs were also quite commonly involved.

The interstitial emphysema involved mainly the anterior and posterior mediastinum, the layers of the pericardium and pericardial fat, the retroperitoneal and especially the perirenal tissues. The absence of inflammation and our inability to find organisms in stained preparations of these tissues, proved to us that the emphysema was not due to a gas bacillus infection. The interstitial emphysema was so uniformly present that we were at first inclined to consider it an artefact. But increased care in the handling and removal of the viscera, the absence of this phenomenon in cases that terminated fatally from causes other than influenza, and the location of the emphysema soon convinced us that this was not the case. The duration of illness in these cases varied from five to fourteen days, and the amount of lung involvement varied from a few bronchopneumonic patches with marked pulmonary edema to complete consolidation of all the lobes of both lungs, so that the vesicular emphysema could not be considered compensatory in nature in every case. Dyspnea and cyanosis were very prominent and constant symptoms, and in most cases altogether out of proportion to the amount of lung involvement.

These questions presented themselves:

1. How did air get into the mediastinal and retroperitoneal tissues?
2. What caused the unusual acute vesicular emphysema?

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* Read before the Section on Pathology and Physiology at the Seventieth Annual Meeting of the American Medical Association, Atlantic City, N. J., June, 1919.

3. What was the cause of the marked dyspnea and cyanosis?

4. What relation, if any, was there between the dyspnea and cyanosis and the emphysema?

The object of the studies recorded in this paper was to reproduce experimentally (in laboratory animals, chiefly rabbits) the essential conditions obtained in the influenza cases and thus, perhaps, find an answer to these questions.

As there was no doubt in our minds that the emphysema in the interstitial tissues was due to an escape of atmospheric air from the lung, we performed the following experiments to determine the path by which such escape took place:

EXPERIMENT SERIES No. 1.—Rabbits were killed with ether. A tracheotomy was then performed and a glass tube connected by means of rubber tubing to a bicycle pump was ligated into the trachea. The pressure used varied from 10 to 15 mm. of mercury.

R1A was inflated by pumping six times in rapid succession. The abdomen became very tight and when opened there was an escape of air. The pumping was repeated and the path of the air observed. With each pumping the air could be seen to fill up the retroperitoneal tissues from above downward and then into the perirenal fat and thighs. The chest was then opened. The sternum was carefully removed causing as little disturbance as possible in the tissues of the anterior mediastinum, to prevent a break in their continuity. There was marked emphysema in the tissues of the anterior, superior and posterior mediastinum and about the loose areolar tissue of the pericardium. The lungs were markedly emphysematous, especially about the margins and at the roots. The chest cavity was then filled with normal salt solution and the pumping resumed. The air could then be observed escaping at the root of the lung in the vicinity of the great vessels and the pleural reflexion.

It is noteworthy that with the chest opened, no air could be forced down below the diaphragm. Presumably with the chest cavity opened the pressure was insufficient to force the air downward. Also a new path of least resistance was created with opening up the chest, namely, externally.

R2A, 3A and 4A were similarly treated, except that the number of insufflations was increased and the interval between decreased. The results were the same as for R1A because a limit is reached beyond which increased pumping produces no further change.

An attempt to photograph some of these animals illustrating the emphysema, proved unsuccessful because of high lights and numerous other technicalities. Most of the air escaped as soon as the continuity of tissues was broken and an avenue of escape thus afforded. Being anxious to secure a photograph we tried out another procedure.

R9A was killed and tracheotomized in the same way. Its abdomen was then opened and the entire animal immersed in 10 per cent. liquor formaldehydi; then he was pumped continually for an hour and fifteen minutes. Our object was to secure fixation of the tissues before the air had a chance to escape. We then opened the chest enough to allow the liquor formaldehydi to enter in order to secure fixation of the thoracic viscera. The animal remained in this solution for two days.

The result was somewhat disappointing, for while there was some emphysema about the great vessels, especially in the region of the kidneys and in the thighs, the amount was negligible as compared with what had been

obtained in the previous animals. The explanation here is probably the same as given for the animal with the opened chest, namely, insufficient pressure, the abdomen having been opened.

Before discussing the route taken by the air in reaching the interstitial tissues, it might be well to review the anatomy of the reflexions of the pleura and pericardium.[1]

The constituent parts of the root of the lung are (1) the two pulmonary veins, (2) the pulmonary artery, (3) the bronchus and (4) one or more small bronchial arteries and veins, the pulmonary lymph vessels and some bronchial glands. Above the root of the lung the

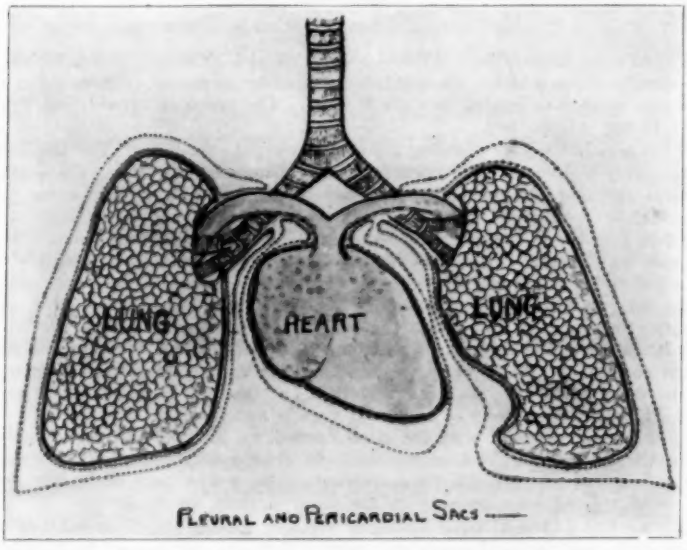

Fig. 1.—Relation of pleura, pericardium and blood vessels illustrating the direct path of the early interstitial emphysema in pericardial fat tissue.

left mediastinal pleura is applied to the arch of the aorta and the phrenic and vagus nerves, to the left innominate veins, to the left superior intercostal vein and the left common carotid and subclavian arteries, to the esophagus and thoracic duct. The right mediastinal pleura, on the other hand, is applied above the root of the lung to the superior part of the vena cava superior and to the right innominate vein, to the innominate artery, to the vena azygos, as it hooks forward above the bronchus, to the vagus and phrenic nerves and to the right side of the trachea. The fibrous pericardium at its apex and posteriorly is gradually lost on the great vessels which enter and emerge

1. Cunningham's Anatomy.

from the heart, giving sheaths to the aorta, the two branches of the pulmonary artery, the superior vena cava, the four pulmonary veins and the ligamentum arteriosum.

This review will aid in mapping our route.

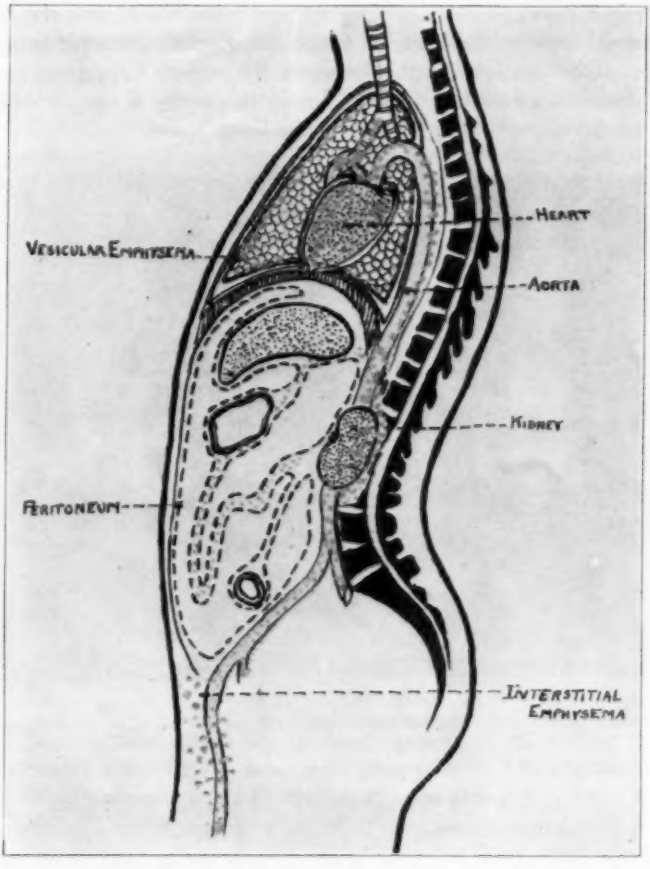

Fig. 2.—Emphysematous paths in relation to the pleurae, pericardium and peritoneum.

First, a vesicular emphysema is produced. Increased intrapulmonary pressure causes rupture of some of the superficial distended air vesicles and there is an escape of air underneath the visceral pleura, which is rather firm. The air finds less resistance in escaping underneath the pleura toward the hilus than to break through it. From the

hilus it travels along the pleural reflexions over the pulmonary arteries and veins to where it meets the pericardial reflexions over the same vessels (Figs. 1 and 2) the tissues of the anterior mediastinum, especially the pericardium and pericardial fat, thence it extends to the superior mediastinum and following the course of the great vessels enters the posterior mediastinum and passes downward into the retroperitoneal tissues—the perirenal tissues being most commonly invaded; it then enters the folds of the omentum, the region of the great vessels and downward into the thighs. Superiorly, some of the air follows the subclavian vessels and enters the axillary space.

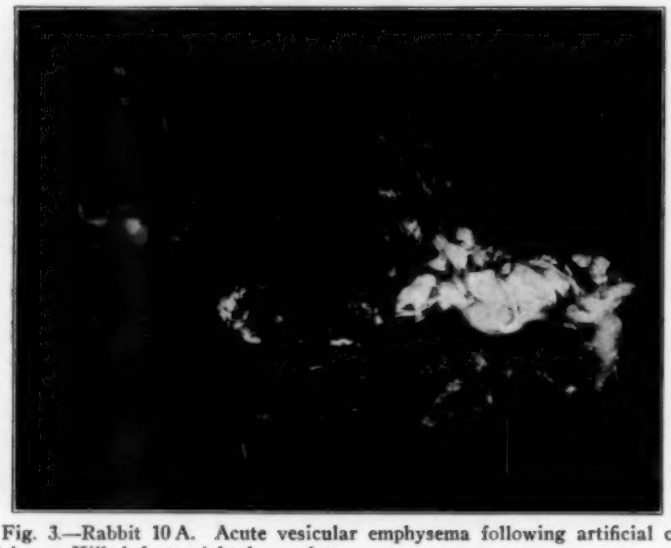

Fig. 3.—Rabbit 10 A. Acute vesicular emphysema following artificial convulsions. Killed forty-eight hours later.

Berkley and Coffen[2] report nine cases of extensive subcutaneous emphysema and spontaneous pneumothorax as a complication of influenzal bronchopneumonia. In their cases the emphysema involved the supraclavicular and infraclavicular spaces, neck, face, arms, chest, trunk, genitalia and thigh. They discuss two possible routes, the intrapleural and the extrapleural. They state that in order for air to pass from the lungs to the chest wall by the intrapleural route, it must pass through both visceral and parietal pleura. To do so, without producing a pneumothorax, it must be assumed that adhesions existed

2. Berkley, Hugh K., and Coffen, T. Homer: Generalized Interstitial Emphysema and Spontaneous Pneumothorax as Complications of Bronchopneumonia, J. A. M. A. **72**:535 (Feb. 22) 1919.

between these membranes at some area, and that the passage of air occurs at this point. At necropsy this seemed the possible route in only one of their cases. They then came to the conclusion that the extrapleural route, as we explained above, is the route taken.

In our experimental cases the intrapleural route is entirely out of the question, as there were no adhesions found at any time. Symmers[3] in discussing the acute vesicular emphysema in post influenzal bronchopneumonia reports three cases of interstitial emphysema. In two cases the soft tissues of the supraclavicular spaces were crepitant with infil-

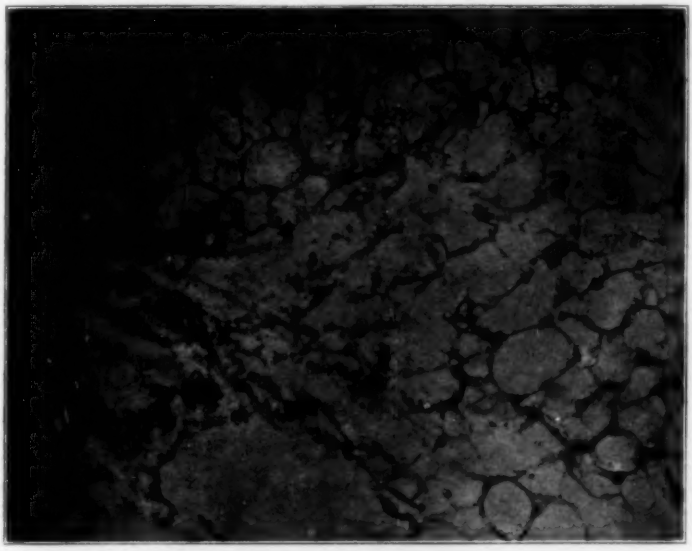

Fig. 4.—Rabbit 5 A. Interstitial emphysema in the tissues of the anterior mediastinum following artificially produced convulsions. Killed thirty minutes after last convulsion.

trated air; in another case the soft tissues of the posterior aspect of the mediastinum were permeated by myriads of emphysematous bullae varying in size from the head of a pin to that of a small marble, air extended thence into the soft tissues of the precordial area downward to the pericardial attachment to the central tendon of the diaphragm, forward into the retrosternal region and thence through the upper apertures of the thorax into the neck and lower portions of the face, downward into the subcutaneous tissues as far as the crest of the

3. Symmers, Douglass: The Pathologic Similarity of the Pneumonia of Bubonic Plague and Pandemic Influenza, J. A. M. A. **71**:1482 (Nov. 2) 1918.

ilium and the lower level of the costal slope on the right. However, he assumes that the interstitial emphysema was due in the first two instances to a rupture of an emphysematous bulla near the apex of the lungs, thus taking the intrapleural route; in the third case the assumption is that an emphysematous bulla ruptured near the root of the lung. In neither case does he mention the presence of any adhesions, nor was he able to find the point of rupture at the necropsy. In his fourth case there was a spontaneous pneumothorax, which was most likely caused by a rupture of a distended vesicle, the air breaking through the visceral pleura.

Fig. 5.—Rabbit 5A. Acute vesicular emphysema.

In our experimental cases we were at no time able to produce an emphysema above the clavicles. This may be explained in two ways—either by a difference in the anatomy between the human and the rabbit, or by a break in continuity of tissues due to the tracheotomy wound.

EXPERIMENTAL SERIES No. 2 had for its object the production of artificial emphysema in living animals and observing its effect on them.

A catheter was connected with a bellows; this catheter was inserted into the trachea and the bellows pumped in such a way as to produce a definite number of respirations per minute, to imitate convulsions, varying in number, as nearly as possible, each convulsion consisting of three respiratory seizures (Table 1).

TABLE 1.—Results of Attempts to Produce Artificial Emphysema in Living Animals

Number	No. Respirations and Time	Respiration per Min.	Seizures in Each Series	Interval between Each Seizure	No. of Series	Interval between Series	Pressure	Remarks
5A	25 in 20 sec.	75	3	30 sec.	1	.....	8-12 mm. Hg.	Four minutes after last artificial respiration, respirations are fifty-eight per minute, deep and labored; ears show cyanosis. Killed thirty minutes after last convulsion. Marginal emphysema; interstitial emphysema in anterior and superior mediastinum and about the pericardium
6A	25 in 20 sec.	75	3	15 sec. first series, 30 sec. second two series	3	7 min. 5 min.	8-12 mm. Hg.	Twenty minutes after last inflation the respirations are irregular, Cheyne-Stokes in character, 128 per minutes. Cyanosis of ears, mouth and about eyes. Ten minutes later respirations are 108, otherwise condition as above Animal seems very thirsty. Forty minutes later killed. Marked marginal vesicular emphysema; interstitial emphysema in anterior and posterior medastinum, about the pericardium in the perirenal tissues in the left side, in the retroperitoneal tissues, along the aorta on the right side, same in the omentum
7A	25 in 20 sec.	75	3	30 sec.	7	5 min.	2 mm.	Respirations were jerky ten minutes after convulsions. Killed twenty minutes after last convulsion. Marginal emphysema, interstitial emphysema about the pericardium
8A	25 in 20 sec.	75	3	30 sec.	7	5 min.	2 mm.	Between intervals the respirations varied from 58 to 115, were quite irregular and jerky, Cheyne-Stokes; sometimes stertorous in character; cyanosis. Killed twenty minutes after last artificial respiration. Marked marginal vesicular emphysema. No interstitial emphysema.
10A	25 in 20 sec.	75	3	30 sec.	3	5 min.	2 mm.	Two hours after last convulsion, marked cyanosis, irregular respirations. Killed forty-eight hours later with one blow so as to avoid a struggle. Emphysema very marked on the margins and at root of lung; some interstitial emphysema about pericardium, otherwise lungs are normal
11A	25 in 20 sec	75	3	30 sec.	3	5 min.	2 mm.	Respirations between seizures irregular, jerky and Cheyne-Stokes in character. Cyanosis. The animal apparently completely recovered in twenty-four hours. Killed five days later by a single blow to avoid a struggle. Very slight marginal emphysema
12A	25 in 20 sec.	75	3	30 sec.	3	5 min.	2 mm.	Symptoms as above. Animal completely recovered in twenty-four hours. Killed six days later. Only very slight marginal emphysema

From Table 1 it will be observed that acute vesicular emphysema can be induced by artificial means (Figs. 3 and 4), that such an emphysema in itself is sufficient to produce dyspnea and cyanosis. According to Torrey and Grosh[4] the pulmonary emphysema interferes with the mass movement of the venous blood thus producing dyspnea and cyanosis.

It will also be noticed that the amount of interstitial emphysema was entirely dependent on the pressure used (Fig. 5). Where a

4. Torrey, Robert G., and Grosh, Lawrence C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Am. J. M. Sc. **157**:170 (Feb.) 1919.

pressure of from 8 to 12 mm. of mercury was used, the air was forced into the mediastinal and retroperitoneal tissues. On the other hand, where the pressure was only 2 mm. of mercury, two or three times the number of so-called convulsions was not sufficient to force much air into the interstitial tissues.

The factors producing the emphysema having been removed the animal recovers within a short time, the air being almost completely absorbed in from six to eight days (Fig. 6).

Fig. 6.—Rabbit 11 A shows almost complete disappearance of the emphysema six days after artificial convulsions were produced.

Experiment Series No. 3.—In the above experiment we found that emphysema will produce respiratory distress (dyspnea and cyanosis). Next we attempted to produce respiratory distress to determine if it in turn will produce emphysema.

R 13 A was sensitized with 0.001 c.c. of egg white. Seventeen days later 1½ c.c. of egg white was injected intravenously. The animal had a violent convulsion two minutes after the injection, another one five minutes later and died in convulsions ten minutes after injection.

The postmortem findings were some marginal emphysema and a small amount of interstitial emphysema about the pericardium and at the root of the lungs (Figs. 7 and 8).

R 14 A was sensitized with ½ c.c of sheep serum. Seventeen days later 2 c.c. of sheep serum were injected intravenously. Three minutes after

Fig. 7.—Rabbit 13 A. Acute vesicular emphysema following an anaphylactic shock.

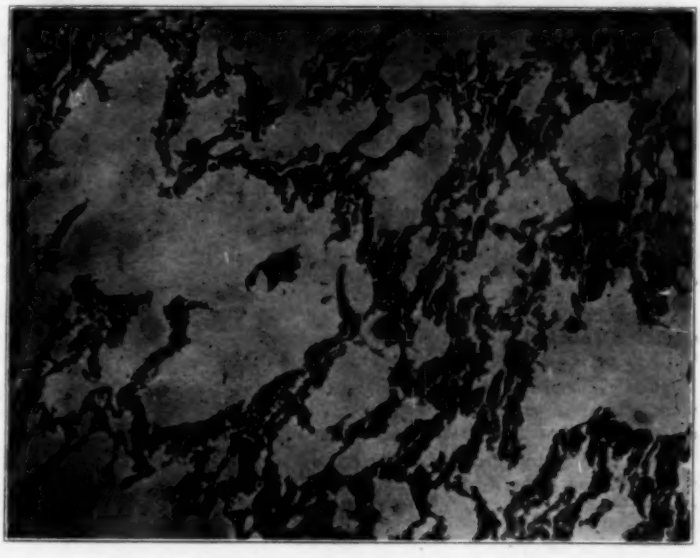

Fig. 8.—A microscopic section from Rabbit 13 A. ×85.

injection the animal cried out as if in great distress; this was followed by a violent convulsion. Eight minutes after injection the animal was dead. The postmortem findings were marked marginal vesicular emphysema, interstitial emphysema in the posterior mediastinum and in the pericardial areolar tissues.

R 15 A was treated the same as R 14 A. This animal had a violent convulsion five minutes after and died eight minutes after injection. Postmortem findings were the same as for R 14 A.

Thus respiratory distress caused by anaphylaxis will produce emphysema. It is fair to assume that respiratory distress from any cause will operate in the same way. Acute vesicular emphysema, on

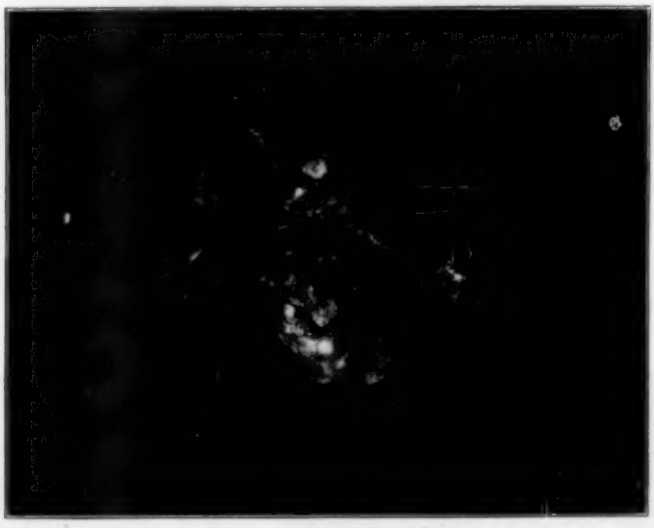

Fig. 9.—Rabbit 23. Vesicular emphysema following injection with influenza toxin.

the other hand, will cause respiratory distress, in a way, producing a vicious circle.

Experimental Series No. 4.—Our last set of experiments consisted in inoculating animals with given amounts of broth cultures of *B. influenzae* (Pfeiffer) or the filtrate of broth cultures.

Out of eighteen rabbits necropsied, fifteen showed varying degrees of vesicular and interstitial emphysema (Figs. 9, 10 and 11). Every one of the animals died in convulsions and marked respiratory distress (Table 2).

Oleate hemoglobin broth, described by Avery[5] as a good culture medium for *B. influenzae*, was used in every case.

5. Avery, O. T.: A Selective Medium for *B. influenzae*—Oleate Hemoglobin Agar, J. A. M. A. **71**:2050 (Dec. 2) 1918.

TABLE 2.—Results of Inoculation with Bacillus Influenzae (Pfeiffer)

No.	Material Injected	Death after Injections	Postmortem Findings
R7	4 c.c. of influenza toxin	1 hr. and 20 min.	Congestion of lungs, marked marginal vesicular emphysema. Interstitial emphysema in tissues of anterior mediastinum, especially about pericardium
R10	7 c.c. of influenza toxin	1 hr. and 30 min.	Marked vesicular emphysema
R11	3 c.c. oleate hemoglobin broth culture	1 hr. and 40 min.	Some vesicular emphysema
R13	2 c.c. oleate hemoglobin broth culture	3 hours	Vesicular emphysema and interstitial emphysema between layers of pericardium
R12	5 c.c. oleate hemoglobin broth culture	5½ days	Lungs markedly congested, some vesicular emphysema, some interstitial emphysema about the pericardium
R5	2 c.c. oleate hemoglobin broth culture	12 hours	All lobes of both lungs were markedly congested. Marginal vesicular emphysema and some interstitial emphysema about the pericardium
R18	4 c.c. oleate hemoglobin broth culture	20 days	(This animal died with symptoms of meningitis.) Lungs perfectely normal except for very marked marginal vesicular emphysema
R19	5 c.c. oleate hemoglobin broth culture	5½ days	Lungs slightly congested, marked marginal vesicular emphysema
R21	3 c.c. filtrate	5 weeks	Small pneumonic patches in both lungs. Vesicular emphysema at the margins and at the root of the lungs. Considerable interstitial emphysema in the anterior mediastinum and in the retroperitoneal tissues along the great vessels
R23	4 c.c. filtrate	11 days	Lower lobes of both lungs congested. Marked vesicular emphysema. Some emphysema in the tissues of the anterior mediastinum
R25	2 c.c. oleate hemoglobin broth culture	36 hours	Vesicular emphysema along the margins and root of lungs. Some interstitial emphysema in the mediastinal and retroperitoneal tissues
R27	2 c.c. oleate hemoglobin broth culture 24 hours later 5 c.c. oleate hemoglobin broth culture	29 hours after first injection	Hemorrhagic spots varying from 1 to 3 cm. in diameter are present throughout both lungs. Marginal vesicular emphysema was present in all lobes of both lungs. Some interstitial emphysema in anterior mediastinum about the pericardium
R28	5 c.c. salt solution suspension	29 hours	Lungs grossly normal except some marginal vesicular emphysema and some interstitial emphysema in the tissues about the pericardium
R29	5 c.c. salt suspension	10 hours	Lungs slightly congested. Some marginal vesicular emphysema and some emphysema in anterior mediastinal tissue
R30	5 c.c. oleate hemoglobin broth culture	10 hours	Marked congestion of posterior aspects of both lungs. Vesicular marginal emphysema

From Tables 1 and 2 it will be seen that emphysema, both vesicular and interstitial, is constantly found postmortem in animals dying after an injection of the *B. influenzae* or its toxin, irrespective of the duration of the illness or the amount of lung involvement.

We have shown in previous experiments that convulsions alone will produce acute vesicular emphysema by producing respiratory distress. But it may be pointed out that respiratory distress alone will not produce the marked emphysema seen in postinfluenzal bronchopneumonia as is shown by pneumonia due to other organisms, where the respiratory distress is apparently just as great. At first glance it would appear that we would have to seek an explanation elsewhere.

Torrey and Grosh[4] found in their cases a destructive softening in the lung parenchyma. Alexander and Follet,[6] in discussing generalized

6. Alexander, M. E., and Follet, E. C.: Subcutaneous Emphysema with the Report of Several Cases, Particularly One with Very Extensive Generalized Emphysema, J. A. M. A. **72**:930 (March 29) 1919.

emphysema in infants, assume that the emphysema is produced by rupture of some of the pulmonary vesicles by a violent exertion or coughing fit, this rupture being due to a congenital weakness of the lung parenchyma. LeCount,[7] after an exhaustive study of microscopic sections of postinfluenzal bronchopneumonic lung, finds marked disseminated necrosis of the alveolar lining as well as of the alveolar capillaries.

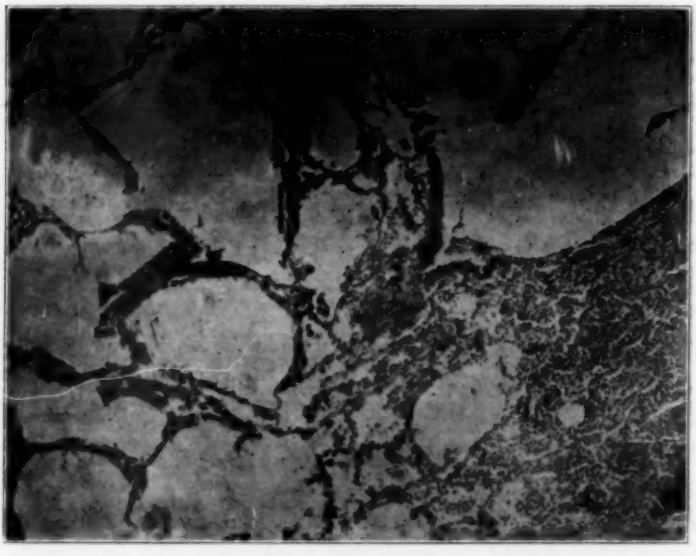

Fig. 10.—Rabbit 19. Showing a bronchopneumonic patch and vesicular emphysema five and a half days after injection with oleate hemoglobin broth culture of *B. influenzae*. ×450.

The evidence cited may account for the discrepancy. However, the time element must be considered. The respiratory distress in lobar pneumonia or bronchopneumonia from other causes, appears comparatively late, when a considerable amount of lung has been thrown out of function, whereas in influenzal infection, dyspnea and cyanosis are almost coincident with the onset of the disease.

One more point must be brought out. The vesicular emphysema is invariably superficial, either on the margins where the lung is very thin, about the root of the lungs, superficially at the apices, or anywhere on the anterior aspect of the lungs superficially. This brings in the mechanical factor. The lung alveoli that are placed centrally,

7. LeCount, E. R.: Disseminated Necrosis of the Pulmonary Capillaries in Influenzal Pneumonia, J. A. M. A. **72**:1519 (May 24) 1919.

are prevented from stretching beyond their limit of elasticity by the surrounding lung tissue; the alveoli more superficially placed lack that support, hence, are the first ones to suffer.

The following explanation seems plausible and fits in with our experimental work. The toxin of the infecting organism or virus, whatever that may be, exerts an irritating influence on the respiratory center, inducing a dyspnea. This assumption is further strengthened

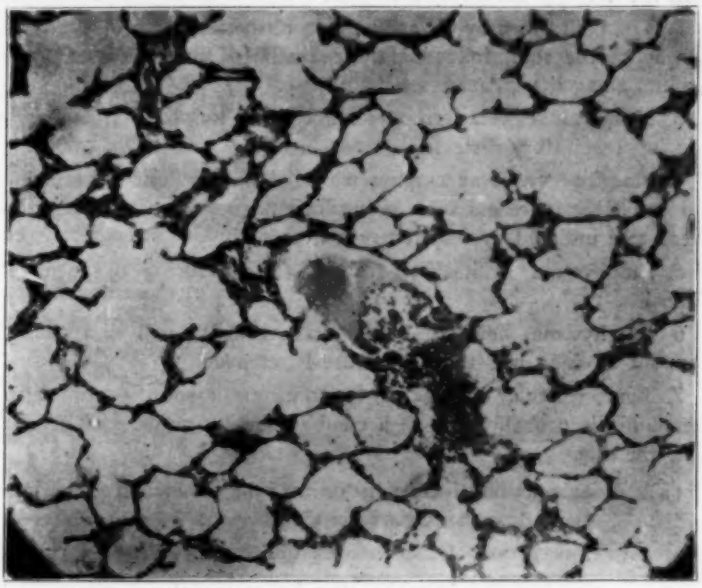

Fig. 11.—Same as Figure 10; more emphysema. ×85.

by the fact that in the epidemic of influenza the pulse was comparatively slow, indicating a possible irritation of the vagus centers, in other words, irritation of the basal ganglia. Dyspnea, as we have shown above, is sufficient in itself to produce emphysema. It is reasonable to suppose that the virus which exerts a toxic action on the respiratory center, also acts locally. Whether the action is due to loss of tone, destruction of lung parenchyma, as pointed out by Torrey and Grosh,[4] or a destruction of the lining of the alveoli, as pointed out by LeCount,[7] is difficult to say. There is no doubt that such action, however it operates, causes a marked weakening of the alveoli.

Respiratory distress on top of weakened alveoli will greatly augment the emphysema. We demonstrated the fact that emphysema in itself will produce respiratory distress and cyanosis. Experimentally,

as soon as the cause is removed, the emphysema disappears in from six to eight days, but in an influenzal infection a vicious circle is established.

CONCLUSIONS

1. Interstitial emphysema as found in our experiments and in fatal cases of postinfluenzal bronchopneumonia is a result of escape of air from the lungs, preceded by a marked vesicular emphysema.

2. The path taken by air escaping from the lung into the tissues is by way of the root, following the reflexion of the pleura and pericardium along the great vessels.

3. Marginal vesicular emphysema can be induced artificially by inducing respiratory distress.

4. Marginal vesicular emphysema as found by our experiments, is a mechanical process due to insufficient support of the marginal alveoli and initiated by respiratory distress.

5. Emphysema in itself is capable of producing dyspnea and cyanosis.

6. Emphysema, both interstitial and vesicular will disappear in from six to eight days after the cause is removed.

7. Acute vesicular emphysema found in fatal cases of postinfluenzal pneumonia is probably due to a combination of causes each intensifying the other.

(a). A toxic action of the virus on the lung parenchyma, causing a marked weakening of the alveoli.

(b). A toxic action of the virus on the respiratory center producing dyspnea and cyanosis, which in itself is sufficient to produce emphysema.

(c). The emphysema thus produced in its turn, increasing the dyspnea and cyanosis.

(d). The above factors combined acting on already weakened alveoli produce the acute vesicular emphysema observed in postinfluenzal bronchopneumonia.

We desire to acknowledge our indebtedness to Dr. Henry Albert, our chief, for very valuable suggestions, and to Dr. Henrietta Calhoun of the department staff, for material aid in handling the animals, assisting with photographs and making the diagrams, and also to Mr. J. Anderson, the department technician, who made all the photographs.

A PRELIMINARY SURVEY OF THE THYROID GLAND AMONG TWO THOUSAND ONE HUNDRED AND EIGHTY-TWO RECRUITS AT CAMP LEWIS, WASHINGTON

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INTRODUCTION

The following survey is based on the examination of 21,182 recruits of the second draft arriving at Camp Lewis, Washington, in April and May, 1918. The survey was taken to determine the number of recruits showing enlargement of the thyroid at the time of induction into the service, and to provide a record in such cases so that changes taking place during training could be more accurately estimated. In addition to making observations as to the size and portions of the thyroid, the occurrence of certain signs and symptoms supposed to be associated with thyroid disease were also noted. The age of the individual, occupation, residence and family history of goiter were noted. These with the objective findings mentioned above form the basis of the report, and will be taken up under their appropriate headings.

In making this survey it was hoped that the data would form a basis to determine the fitness of recruits with thyroid enlargement for general military service, and furthermore whether any particular group of cases withstood the rigor of training better than others. Incidentally, the survey has afforded an opportunity to study the geographic distribution of endemic goiter in a large area of the United States.

My attention was first particularly called to the question of thyroid disease in the army during the fall and winter of 1917 and 1918 when the soldiers were undergoing intensive training. At that time very few cases of organic heart disease were being referred to the cardiovascular examiner but a large proportion of the referred cases presented rather significant functional disorders or many of the signs and symptoms of the syndrome described by Dr. Thomas Lewis under the term "Neurocirculatory asthenia." The frequency of thyroid enlargement in these cases was also noted, and it seemed that the frequent association was too common to lack significance. In these

* President of the cardiovascular board when the survey was made.

cases the enlargement of the thyroid was not marked and had, therefore, not attracted particular attention at the time of mustering into service, thus without a record of the condition at the time of induction into the service, no estimate of the changes taking place under training could be made.

The examinations were made within the first few days after the recruits reported at camp, at the time when the examinations were made by the special examining boards. One of the cardiovascular examiners was detailed for this duty. I wish to express my appreciation to Lieut. Carl P. Moran, M. R. C., who assisted in making the examinations, but who was ordered elsewhere before the survey was completed, and to contract surgeon Thomas Addis for his assistance throughout. A uniform method for the examination was adopted. The subjects, stripped to the waist, passed by in single file. If there was no obvious enlargement of the thyroid gland on swallowing, the examiner placed a thumb on each side of the neck just below the cricoid cartilage and the subject was asked to swallow again. By this latter method definite enlargements were often noted which were not revealed by inspection. Following the examination of the thyroid gland the presence or absence of eye signs, tremor, tachycardia, vasomotor instability, moist skin, curved nails and clubbing of the fingers were noted. The findings were dictated to a clerk who passed the subject on to another clerk who completed the record of name, age, residence, occupation, family history of goiter, etc., as per attached form.

PRELIMINARY GOITER STUDY

Date.....1918

Drafted from: Town: County: State:
Name Rank Co. Regiment:
Age Occupation Wages
Residence the past year: Birthplace:
Family history of goiter: Father Mother Sister Brother

SYMPTOMS

Dyspnoea	Nervousness	Loss in weight
Weakness	Headache	Diarrhoea
Palpitation	Dizziness	Constipation
Pain around heart	Apprehension	Polyuria
Sweating	Insomnia	

When goiter appeared Changes in size Pressure symptoms

FINDINGS

Type of individual:		Asthenic	Normal	Sthenic
Size of thyroid		Small	Moderate	Large
Character of tumor:	Firm	Soft	Hard	Nodular
Portion involved:	Isthmus	Right lobe	Left lobe	Diffuse
Tremor:		Vaso-motor instability		
Eye signs		Heart findings		
Clubbing of Fingers		Curved nails		
Pulse rate:		Mottling of skin		

Diagnosis: Accept Domestic service only Reject

TOTAL NUMBER AND PERCENTAGE OF RECRUITS WITH ENLARGED THYROIDS

Among 21,182 recruits, 4,693, or 21 per cent., were found to have "enlarged thyroids."

In considering these figures it is important to bear in mind our definition of what constituted thyroid enlargement. Any man in whom the gland or any part of it could be felt deistinctly on swallowing was classed as having an enlarged thyroid. This definition was, of course, recognized as being an altogether arbitrary one. It was adopted because for our statistical purposes it seemed essential to have a sharply defined standard. But it is clear that our total figures must include many cases in which the limits of the physiologic variation in the size of the thyroid were not exceeded, and which were classed as instances of enlargement because a thin neck or poorly developed muscles made it easier than usual to feel the gland. On this account the classification of these cases according to the degree of enlargement in subsection A is of particular significance.

TABLE 1.—THE NUMBER AND PERCENTAGE OF LARGE OR MODERATELY ENLARGED AND OF SMALL THYROIDS IN 4,693 CASES OF ENLARGED THYROIDS FOUND IN 21,182 RECRUITS

Size	Number	Percentage
Large and moderately enlarged	1,276	27
Small	3,417	73

Degree of Enlargement.—In Table 1 it is shown that of the 4,693 cases of "enlarged thyroids," 27 per cent. were classed as moderately or greatly enlarged, and 73 per cent. as instances of a small degree of enlargement. The smaller class includes only cases in which the thyroid enlargement was so manifest that no element of judgment entered into its recognition. This, then, was a uniform group of cases clearly marked off by the existence of a striking anatomic abnormality. On the other hand, the larger class is composed of a mixture of cases in which there was almost certainly an increase in the size of the thyroid and of cases in which there was almost certainly no enlargement. While in the first group the enlargement was certain, in the second there was a variation through all degrees between a high degree of probability to a bare possibility of enlargement.

By restricting attention only to those cases in which the enlargement was certain the true incidence of endemic goiter is doubtless greatly underestimated, yet even so the number of such cases (1,276) is surprisingly high and constitutes nearly 6 per cent. of the total number of recruits examined.

TABLE 2.—The Part of the Thyroid Gland in Which Enlargement Was Noted

Location	Number	Percentage
Diffuse	1,776	38
Isthmus	2,417	52
Right lobe	259	5
Left lobe	192	4

Table 2 shows that in 38 per cent. of the cases the enlargement was noted as diffuse, in 5 per cent. as being mainly or entirely an enlargement of the right lobe and in 4 per cent. of the left lobe. The remainder, or 52 per cent. of all the cases, are given as enlargements of the isthmus. The large proportion of isthmus cases is of course due to the fact that in the lesser degrees of enlargement, it was only the isthmus which could be felt. In most of these cases the probability is that the enlargement was more or less uniform in all parts of the gland.

C. Distribution of Goiter in the Families of Recruits with Thyroid Enlargement.—Table 3 gives the percentage of goiters in the members of the families of the recruits with thyroid enlargement. These data were compiled from the statements of the recruits.

TABLE 3.—Distribution of Goiter in the Families of 4,693 Recruits with Thyroid Enlargement as Obtained from Their Histories

Members of Family	Number	Percentage
Sisters	554	52
Mothers	311	29
Brothers	172	16
Fathers	33	3

Among the four categories of this table, a comparison is possible between the percentage of sisters and brothers affected, since the total numbers of sisters and brothers were probably approximately the same. The figures show that there were more than three times more sisters than brothers affected. Similarly, a comparison may be drawn between the incidence of goiter in mothers and in fathers. Here the difference is still more marked, 311 mothers as opposed to only thirty-three fathers with goiter. These cases probably include only cases in which the goiter was particularly prominent, for most of the men came from districts where endemic goiter is so prevalent, that minor degrees of enlargement are apt to be considered as within the range of normality.

D. Age Distribution in Recruits with Thyroid Enlargement.—In making the survey the age of individuals with enlargement of the thyroid gland was noted in 4,290 cases out of 4,693 recruits with enlarged thyroids. The number of cases by years and percentage by years is recorded in Table 4.

TABLE 4.—NUMBER OF CASES BY YEARS OF AGE

Age	No. of Enlarged Thyroids	Per Cent.
21	33	0.8
22	622	14.5
23	680	15.85
24	550	12.8
25	479	11.2
26	432	10.1
27	383	8.9
28	335	7.8
29	323	7.5
30	208	4.85
31 and 32	245	5.7
Total	4,290	100.0

The figures show that there were very few cases in the twenty-first year. This is due to the fact that in April and May, 1918, when the recruits were inducted into the service there were very few men of the 1917 registration who had not reached their twenty-second birthday. The figures for thirty-one years are larger than for the thirtieth year because it includes all men who were 31 years of age and those who had passed their thirty-first birthday when they were inducted into the service. The largest number of enlarged thyroids was noted in men 23 years of age. The lower figure for those of 22 years of age is possibly caused by an increased voluntary enlistment of men under their twenty-third year.

In order to determine whether the decrease in the percentage of thyroids after the twenty-third year is apparent or real, the records of 2,000 unselected recruits were reviewed. The number and percentage of men from 21 to 31 years of age are recorded in Table 5.

TABLE 5.—NUMBER OF MEN AT VARIOUS AGES

Age	No. of Recruits In Given Age	Per Cent.
21	15	0.75
22	268	13.4
23	287	14.35
24	252	12.6
25	222	11.1
26	200	10.0
27	167	8.35
28	190	9.5
29	158	7.9
30	108	5.4
31	133	6.65
Total	2,000	100.0

A comparison of the above percentages with those for enlarged thyroids with ages shows that the decrease in the number of thyroids from 21 to 31 years of age is only apparent. It appears definitely shown that there is no decrease in the number of cases of thyroid enlargement between 21 and 31 years of age. The following curve illustrates the point better.

E. The Incidence of Certain Abnormal Physical Signs in Individuals with Thyroid Enlargement.—Statistical data were collected on the frequency of certain signs in cases of goiter. The selection for study of the particular signs defined below was based on the previous experience of the Board in the examination of cases of thyroid enlargement referred to it on account of various complaints or defects. This experience had given rise to a seemingly well founded impression that

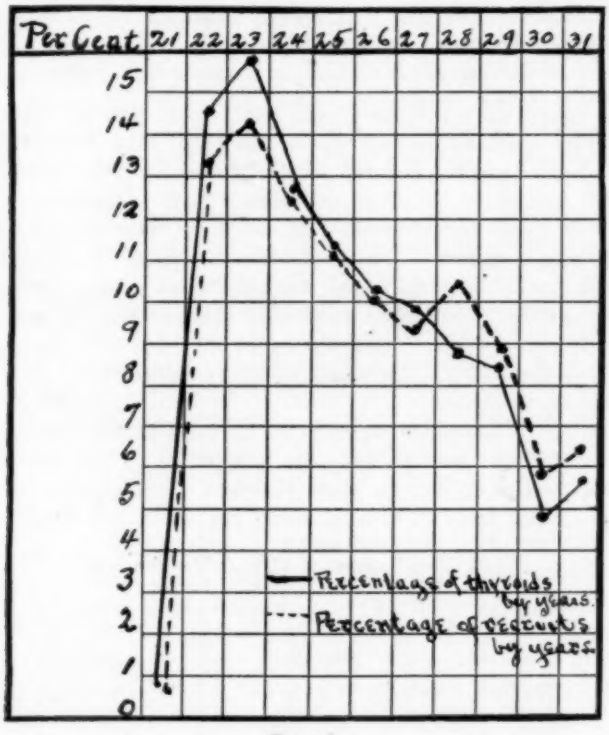

Chart 1

there was a relation between thyroid enlargement and the occurrence of several of the following objective abnormalities: (1) Tachycardia; (2) systolic murmur in the pulmonary area; (3) a second sound louder in the pulmonary than in the aortic area; (4) tremor; (5) moist blue hands, and (6) curved fingernails.

Limitations arising from the conditions under which the data had to be collected prevented the study of all these signs at this time. Only one member of the board could be spared from routine duties.

Since the primary object of the examination was to record all cases of enlarged thyroid and to determine the frequency of the condition in the total draft, it was necessary to examine every man. Thus, more than one thousand recruits commonly passed through the examiner's hands every day, and it was not found possible to make records of pulse rate or to examine with sufficient accuracy for the absence or presence of the auscultatory cardiac signs which it was supposed might have some association with the thyroid enlargement. Experience soon showed that one man could not do more than record the absence or presence of goiter and note in those cases in which it was present whether the enlargement came under the terms small, moderate or large as defined in the previous section, and whether the enlargement was diffuse or apparently localized to the isthmus or the right or left lobes. After this there was time only to note the absence or presence in goiter cases of tremor, moist blue hands and curved nails.

In addition to the limitations imposed by the shortness of the time available for the examination, there was another arising from the fact that the great majority of the men had received their first injection of typhoid vaccine at some time within the twenty-four hours preceding the examination. The constitutional disturbance arising in many of the men from this cause was, as we found later, a considerable factor in determining the frequency of the above signs. It was early recognized also that pulse rates obtained under these circumstances could have only a very limited significance.

The meaning of the figures obtained by this examination can of course only be determined by comparison with those obtained from a group of individuals observed under the same conditions who had no thyroid enlargement. Similar data were therefore also collected from as many nongoiter individuals as time allowed.

In view of the necessarily unfavorable conditions attending the examination the board does not regard the figures relating to the incidence of tremor, etc., as in the nature of more than a rough preliminary survey. The main object was to determine the frequency of endemic goiter in men coming to Camp Lewis. The further study of various signs present in cases with thyroid enlargement is now being undertaken in men of the June and July drafts and will be reported later.

DEFINITION OF SIGNS

There is a large personal factor in dealing with such signs as tremor, moist blue hands and curved nails, even though no attempt is made to attach any quantitive value to them. It is therefore of great importance that all the work be done by one man. This unfortunately was not possible, since Lieutenant Moran, who commenced the work,

was ordered elsewhere before it was completed. In spite of an attempt to conform to the same standards, the figures of his successor varied appreciably from those obtained by him. No absolute value can therefore be attached to the figures given. Greater significance, however, is found in the comparison of the incidence of these signs in nongoiter as opposed to goiter cases, and here there was a uniformity of standards for the same observer saw all the members of both groups.

TREMOR

The arm was extended at right angles to the body with the fingers extended. The very slight tremor which is not uncommon in apparently normal individuals and which is somewhat difficult to make sure of, was disregarded. Very coarse, incoordinate movements of individual fingers were also ruled out. It was found that a distinct tremor was sometimes present in only one finger, commonly the index finger, and was absent in others. These cases were not counted.

Of the total number of men with enlarged thyroids 2,591, or 55.0 per cent., had tremor.

MOIST, BLUE HANDS

The incidence of this sign naturally varies considerably with changes in the temperature and humidity of the air. Those cases were counted in which there was a clearly apparent degree of cyanosis of the hands, and in which palpation of the palms revealed a definite moisture.

Of the total number of men with enlarged thyroids 4,123, or 88.0 per cent., had moist, blue hands.

CURVED NAILS

By curved nails is meant an anteroposterior curving which was present to a marked degree not only in the first and second but also in the third and fourth finger nails.

Of the total number of men with enlarged thyroids 2,612, or 56.0 per cent., had curved finger nails.

COMPARISON OF THE INCIDENCE OF TREMOR, MOIST, BLUE HANDS AND CURVED NAILS IN GROUPS OF MEN WITH AND WITHOUT THYROID ENLARGEMENT

This comparison entailed such a considerable increase in the amount of work that the examination had to be very hurriedly conducted in order to prevent delay in the passage of men from one examining board to the other. For this reason it was not possible to carry this through as a routine. The percentage figures for the two groups are given in Table 6.

The results of this comparison were not those expected by the Board. The impression had been gained that the above signs were much less frequent in nongoiter cases than is actually shown by these figures. This fact seems to make it all the more important that more accurate data under more satisfactory conditions of examination be obtained as to the relative incidence of these signs. A report of this more detailed examination will be forwarded shortly.[1]

TABLE 6.—COMPARISON OF A GROUP OF 1,138 RECRUITS WITHOUT THYROID ENLARGEMENT AND OF A GROUP OF 1,397 RECRUITS WITH THYROID ENLARGEMENT AS REGARDS THE PERCENTAGE FREQUENCY OF CERTAIN SIGNS

Sign	Nonthyroids	Thyroid
Tremor	44.0	54.0
Moist, blue hands	76.0	95.0
Curved nails	64.0	75.0

GEOGRAPHICAL DISTRIBUTION

F. State Distribution.—The geographic distribution outlined in the tables and maps of this section refers only to the distribution of enlarged thyroids, as we have defined that term, in men between the ages of 21 and 31. But it may be noted that the distribution throughout the whole population will relatively correspond closely with that which we have deduced from this special section of the community.

The distribution among the various states of all cases classed as having enlarged thyroids is given in Table 7.

TABLE 7.—THE NUMBER AND PERCENTAGE OF ENLARGED THYROIDS IN RECRUITS FROM DIFFERENT STATES ARRANGED IN ORDER OF DESCENDING MAGNITUDE

State	Percentage Enlarged Thyroids	No. of Enlarged Thyroids	No. of Recruits
Washington	39	826	2,114
Oregon	32	291	923
Montana	26	900	3,465
Idaho	26	362	1,395
Wyoming	25	128	516
Minnesota	22	1,023	4,714
Utah	22	318	1,434
North Dakota	17	212	1,230
South Dakota	14	252	1,848
Nevada	9	17	179
California	8	360	4,364

Washington and Oregon show the highest percentage, and Nevada and California the lowest.

On account of the fact mentioned in the previous section that under our particular definition many cases were included in which the seeming enlargement of the thyroid may not have been pathological, special

1. Addis, Thomas, and Kerr, William J.: Arch. Int. Med. **23**:316 (March) 1919.

attention is directed to Table 8, which gives the percentage in the different states of cases in which the thyroid was certainly enlarged far beyond any physiological limit.

TABLE 8.—The Number and Percentage of Large or Moderately Enlarged Thyroids in Recruits from Different States Arranged in Order of Descending Magnitude

State	Percentage of Large or Moderately Enlarged Thyroids	No. Large or Moderately Enlarged Thyroids	Total No. Recruits
Washington	11.0	232	2,114
Oregon	8.6	79	923
Idaho	7.3	102	1,395
North Dakota	6.6	81	1,230
Montana	6.4	222	3,465
Utah	5.5	79	1,434
Minnesota	5.1	242	4,714
Wyoming	3.7	19	516
South Dakota	2.0	37	1,848
Nevada	1.1	3	179
California	0.5	23	4,364

It will be noted that the arrangement of the states is still the same at the extremes, but that the relative difference between such states as Washington and California is more pronounced when only grossly enlarged thyroids are dealt with. In Tables 9 and 10 are given the state distribution as regards the part of the thyroid gland in which enlargement was noted, and the incidence of goiter in the families of recruits with thyroid enlargement.

TABLE 9.—The Portion of the Thyroid Gland in which Enlargement Was Noted in Recruits from Different States

State	Percentage			
	Diffuse	Isthmus	Right Lobe	Left Lobe
Washington	61	32	4	3
Oregon	55	39	3	3
Montana	41	53	4	2
Idaho	57	35	5	3
Minnesota	21	58	11	9
Wyoming	48	50	1	1
Utah	28	35	5	3
North Dakota	30	67	2	1
South Dakota	25	72	2	1
Nevada	45	55	0	0
California	40	54	4	3

TABLE 10.—Distribution of Goiter in the Families of Recruits with Thyroid Enlargement from Different States

State	Sister	Mother	Brother	Father
Washington	50	27	20	3
Oregon	58	20	21	1
Montana	47	35	17	2
Idaho	48	33	17	2
Minnesota	55	28	13	3
Wyoming	52	28	14	7
Utah	53	26	15	5
North Dakota	57	31	8	4
South Dakota	55	37	8	0
Nevada	80	20	0	0
California	39	37	21	4

The relative distribution of enlarged thyroid glands among the different states is represented by means of different depths of shading in Chart 2.

CONCLUSIONS

1. A survey of 21,182 troops coming to Camp Lewis, Washington, from eleven states, comprising an area of approximately one third of the United States, shows a high incidence of simple goiter in certain regions. The incidence is highest in Washington and Oregon, and lowest in California and Nevada. There is an area of endemic goiter largely confined to the Pacific Northwest, and shading off to the south

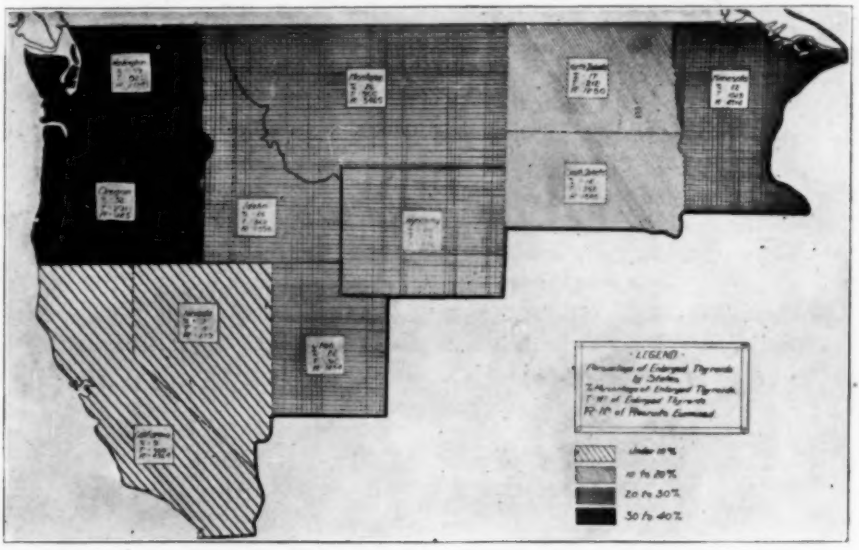

Chart 2.—Relative distribution of enlarged thyroid glands among different states.

and east. There is again a slight increase in Minnesota which should be considered as a part of the endemic goiter region adjacent to the Great Lakes.

2. Exophthalmic goiter was very rarely seen in troops coming to this camp, although many recruits were rejected because of thyroid enlargement producing pressure symptoms or interfering with the wearing of the military collar. Cases of exophthalmic goiter were rejected by the local boards.

3. Twenty-one per cent. of all troops examined showed a definite enlargement of the thyroid gland. Of these, 27 per cent. showed a

large or moderately enlarged thyroid, and 73 per cent. were classified as "small." In the latter group only those in whom the gland could be distinctly felt on swallowing were included.

4. The enlargement of the thyroid gland was noted as diffuse in 38 per cent. of the cases, isthmus in 52 per cent., right lobe in 5 per cent., and left lobe in 4 per cent.

5. The family history of recruits with enlarged thyroid glands showed that goiters had been noted in sisters three times more frequently than in brothers, and in mothers ten times more frequently than in fathers.

6. There was no evidence to show that the thyroid gland diminishes in frequency between the ages of 21 and 31 years.

7. Such physical signs as tremor, tachycardia, vasomotor instability of the hands and curved nails, were noted, and were found in a larger percentage of men with thyroid enlargement than in those without demonstrable changes in the thyroid. The differences, however, were not striking, and no definite conclusions can be drawn at this time.

8. No definite conclusions can be drawn as to the etiologic factors in the production of endemic goiter. The region affected roughly corresponds to the glaciated areas of the United States. There is apparently some relation to the water supply.

9. The geographic distribution has been shown by states. Similar statistics by counties in each state have been compiled, but for want of space are not included in this report.

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